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VOLUME 245 OCTOBER 4, 1951 NUMBER 14

Diabetic Nephropathy 513
James Lee Wilson, Howard F. Root and Alexander Marble

Amelioration of Diabetes and Striking Rarity of Acidosis in Patients with Kimmelstiel-Wilson Lesions 518
Charles G. Zubrod, Stanton L. Eversole and George W. Dana

The Use of Tantalum Mesh in Chest-Wall Defects 525
J. Murray Beardsley and Charles R. Cavanagh, Jr.

Development of Neurologic Manifestations of Pernicious Anemia During Multivitamin Therapy 529
C. Lockard Conley and Julius R. Krevans

Medical Progress: Antihistamines: Their Use and Abuse 532
Walter S. Burrage

Case Records of the Massachusetts General Hospital 537

Editorials:
Studentibus Medicinae Internisque 545
Pernicious Anemia and Multivitamin Preparations. 545
1952 Prize-Essay Competition 547

Massachusetts Department of Public Health . 547

Correspondence 547

Notices 547

Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879.

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*Baumgartner, L.: Wider Horizons for Children; The Mid-century White House Conference and Children's Nutrition, J. Am. Dietet. A. 27:281 (Apr.) 1951.

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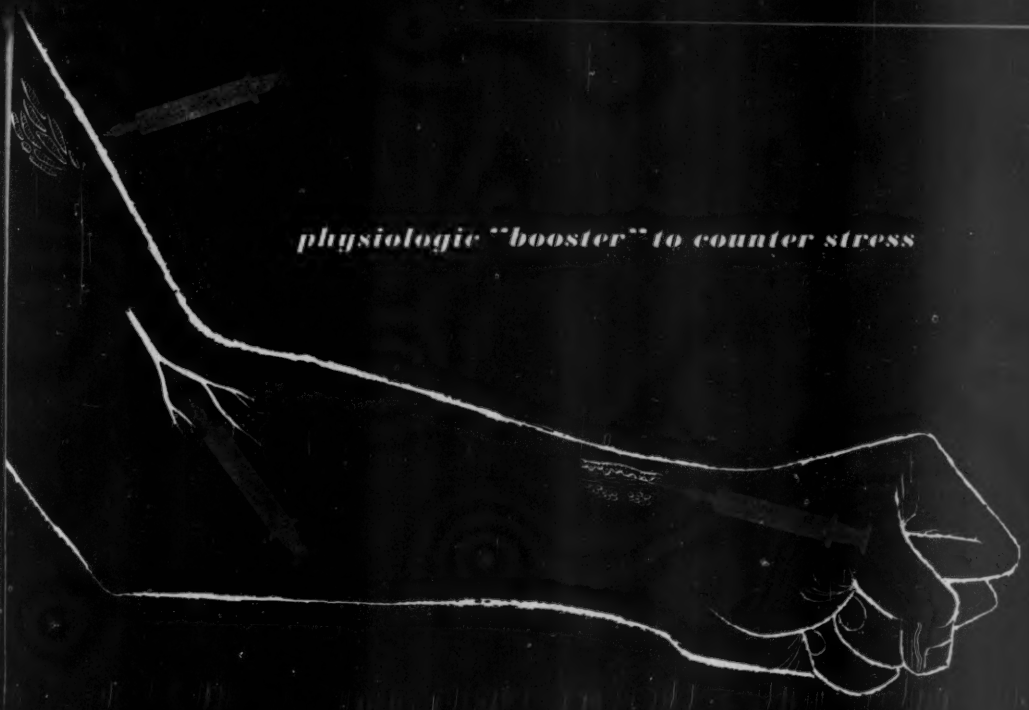

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Studies in psychosomatics have shown that functional disorders often are a result of the patient's inability to adjust to emotionally stressful situations (stressor factors).

Nervous tension and chronic anxiety, discharged through a labile Autonomic Nervous System, can cause somatic disturbance. [1,2] Such states may involve any one of the organ systems or several at one time. [1,3] The outline below is designed to relate gastrointestinal and cardiovascular symptomatology to the exaggerated response of the autonomic nervous system.

	Physiologic Effects of Autonomic Discharge	
	Sympathetic	Parasympathetic
Gastro-intestinal System	Hypomotility Intestinal Atony Hyposecretion Reduced salivation	Hypermotility Gastrointestinal spasm Hypersecretion
Cardio-vascular System	Rapid heart rate Peripheral vaso-constriction	Slow heart rate Vasodilatation
Functional Manifesta-tions	Palpitation Tachycardia Elevated blood pressure Dry mouth and throat	Heartburn Nausea-vomiting Low blood pressure Colonic spasm

The data here tabulated is from references 2,4,5,6,7, given below.

When the clinical picture is suggestive of functional disorder, the diagnosis is supported by the presence of the following indications of autonomic lability:

Variable Blood Pressure
Body Temperature Variations
Changing pulse rate
Deviations in B. M. R.
Exaggerated Cold Pressure Reflex
Oculo-Cardiac Reflex Abnormalities
Glucose Tolerance Alterations

Therapy in these cases is directed toward: 1) relieving the somatic disturbance to prepare the patient for psychotherapy*; 2) guidance in making adjustment to stressful situations and correction of unhealthy attitudes.

*Drug treatment using adrenergic and cholinergic blocking agents in conjunction with sedatives. [8,9,10.]

1. Ebaugh, F.: Postgrad. Med. *4:* 208, 1948. 2. Wilbur, D.: J.A.M.A. *141:* 1199, 1949. 3. Williams, E. and Carmichael, C.: J. Nat'l. Med. Assoc. *42:* 32, 1950. 4. Goodman, L. and Gilman, A.: The Pharmacological Basis of Therapeutics, The Macmillan Co., 1941. 5. Katz, L. et al: Ann. Int. Med. *27:* 261, 1947. 6. Weiss, E. et al: Am. J. Psychiat. *107:* 264, 1950. 7. Alvarez, W.: Chicago Med. Soc. Bulletin, 581, 1950. 8. Rakoff, A.: A Course in Practical Therapeutics, Williams and Wilkins, 1948. 9. Karnosh, L. and Zucker, E.: A Handbook of Psychiatry. C. V. Mosby Co., 1945. 10. Harris, L.: Canad. M.A.J. *58:* 251, 1948.

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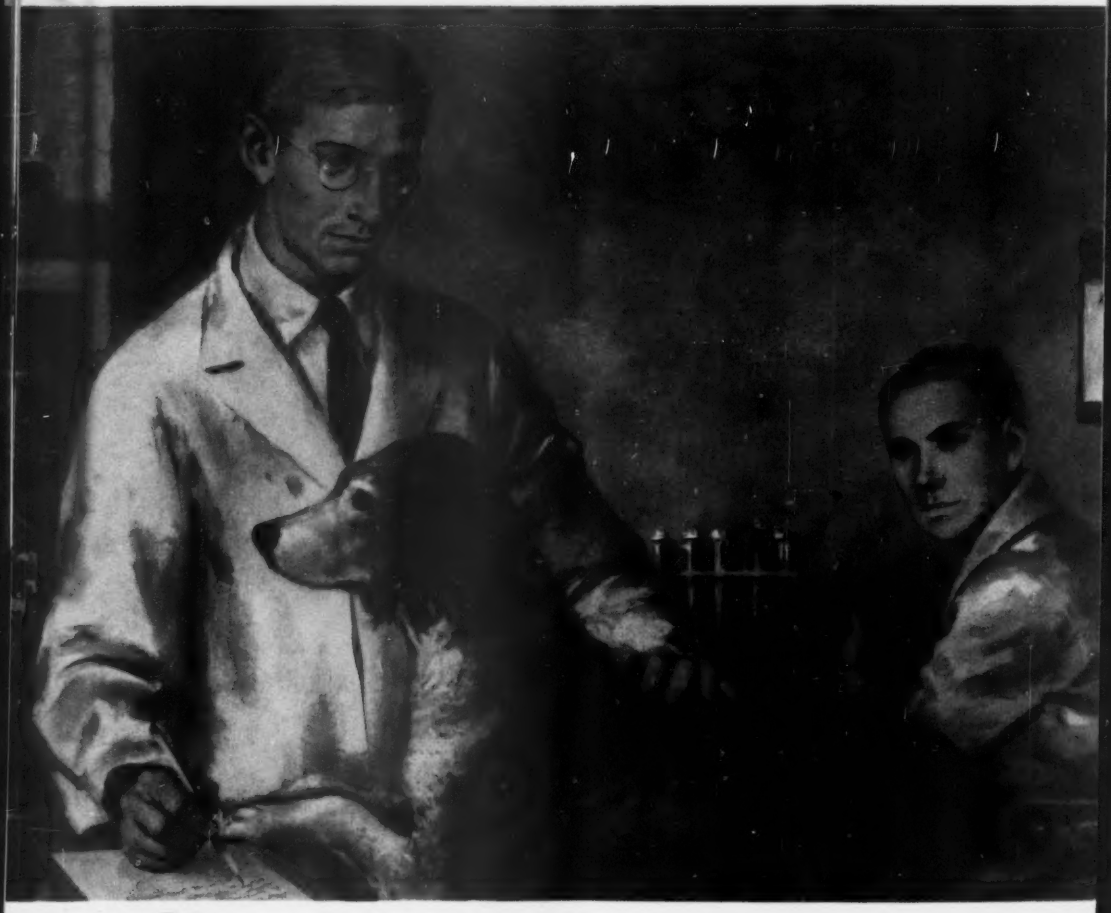

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Volume 245 OCTOBER 4, 1951 Number 14

DIABETIC NEPHROPATHY*

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JAMES LEE WILSON, M.D.,† HOWARD F. ROOT, M.D.,‡ AND ALEXANDER MARBLE, M.D.§

BOSTON

SINCE the publication of the report by Kimmelstiel and Wilson[1] in 1936, much has been written and said about the intercapillary glomerulosclerosis seen frequently at post-mortem examination in older diabetic patients. Porter and Walker,[2] Henderson, Sprague and Wagner,[3] Rifkin and his co-workers[4] and others[5-7] have presented excellent discussions of the clinical picture considered to be due to such lesions. However, we have been impressed by the fact that in diabetic patients, both young and old, intercapillary glomerulosclerosis rarely if ever occurs as an isolated lesion and often seems relatively unimportant or may even be lacking. The renal involvement is almost invariably of mixed etiology, including both degenerative and infectious elements. It has seemed to us preferable to designate the clinical syndrome as "mixed nephropathy associated with diabetes" or, more concisely, "diabetic nephropathy," rather than to attempt to ascribe the entire clinical picture to glomerulosclerosis alone.

Although diabetic nephropathy of mixed etiology is common in older patients as well, this communication concerns young patients with severe, poorly controlled diabetes of long duration. In this group it is responsible for more deaths than all other causes. Prior to 1937 only 2 per cent of deaths among such patients were due to renal disease.[8] However, a review of the clinical records of 135 young patients with onset of diabetes under the age of fifteen years who died during the period 1944-1950 showed ante-mortem renal damage of advanced degree to have been present in at least 72 cases, or 52 per cent of the group.[9] These changes have been observed to occur concomitantly with the spectacular increases during recent years in the life expectancy of young patients with diabetes. Those patients who formerly died early in life of coma or acute infections are now avoiding or surviving these perils through the judicious use of insulin and antibiotics, only to succumb several years later to complications reflecting degenerative vascular disease. Although vascular disease in general manifests itself throughout the entire body, the resulting functional impairment may be localized predominantly to a single organ or site. Such is the case among these young patients with diabetes who live for months or years with gradually increasing evidences of vascular disease, which, though generalized, impair renal function most severely. Renal disease is responsible for the majority of the symptoms experienced by these patients before death, which most commonly occurs in uremia, although the terminal event may be a coronary occlusion or a cerebrovascular accident.

Sixty-two patients, or 25 per cent, of a group of 247 recently reviewed cases of long-standing diabetes in young persons showed manifestations of diabetic nephropathy.[10] These 62 patients were studied in more detail, since numerous observations that were made differed considerably from those recorded in the literature in many articles concerning renal disease in diabetes. The various manifestations observed among these 62 cases were correlated with the histopathological findings in those fatal cases in which an autopsy was performed and were compared with the reported observations of other investigators. Furthermore, all these patients were studied in order to evaluate the relation between their renal status and the degree of control of their diabetes.

It is the purpose of this paper to present the characteristic clinical manifestations of diabetic nephropathy and to describe their chronologic development and the associated histopathological findings.

METHODS OF STUDY

A comprehensive review of the findings in the entire group of 247 patients appears in a separate paper.[10] All subjects were young patients with

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severe diabetes that had had its onset between the ages of eighteen months and thirty years and had been present for ten to thirty-four years. All patients were studied carefully by means of laboratory procedures and clinical examinations designed to evaluate the status of their cardiorenal vascular system. Renal function was studied by determinations of phenolsulfonphthalein excretion, urea clearance, microscopical examination of the urine sediment and quantitative measurement of proteinuria. Simple but relatively rigid standards of control were established and utilized to evaluate the type of treatment and degree of control followed by each patient in the management of his diabetes.

Observations

With few exceptions, the various clinical manifestations in the patients under study were observed to occur in relatively the same chronologic order. All of the 62 patients had shown proteinuria as one of the earliest and most constant manifestations, and in 45 of these large amounts of protein, 100 mg. per 100 cc. or more, were repeatedly observed in the urine. An abnormally increased capillary fragility index (modified Göthlin technic) was found in 39 of the 43 patients so tested. Retinitis was observed in 55 patients, of whom 18 were found to have retinitis proliferans. Hypertension (a blood pressure of 150/90 or above) was present in 41 patients. Thirty-seven patients were anemic (a hemoglobin of less than 12 gm. per 100 cc.). Vascular calcification was demonstrated by roentgenogram in 47 cases, or more than 75 per cent of the group, and was considered to be moderately or markedly extensive in 37 patients.

Doubly refractile lipoid bodies were observed on repeated occasions in acidified urine specimens from many of these 62 patients with renal involvement. The clinical significance of these anisotropic cells has been thoroughly reviewed by Rifkin and his co-workers.[4]

A "typical" case of diabetic nephropathy can be illustrated by the following chronology of events:

A child of twelve to fifteen years of age is found to show cardinal symptoms of diabetes that have been present for only a few days to weeks. A diagnosis of diabetes mellitus is made and the condition brought under control by treatment with diet and insulin. Regulation is carried out either during a hospital stay or at frequent visits to the physician's office or out-patient department. The child and his parents are carefully instructed concerning the management of the newly discovered disease.

Strict compliance with the instructions given about diet and insulin is maintained by the child's parents during the first few months. Gradually carelessness born of familiarity and monotony begins to creep into the management of the child's condition, and as the years pass gross neglect ensues, particularly beyond the age of fifteen or sixteen, when the child has less parental supervision. There may be one or more episodes of diabetic coma, from which the patient is revived, perhaps with relatively little difficulty. After ten to twelve years of such treatment the patient, now in his early thirties, is found to show proteinuria during one of his infrequent visits to the physician. Further examination reveals this to be intermittent in occurrence but associated with an abnormal increase in the capillary fragility index, and an occasional punctate hemorrhage or microaneurysm is observed in the periphery of the retina. Although disturbed by the presence of these new developments, the patient does not become concerned enough to improve his present inadequate management. Eighteen to twenty-four months later many signs and symptoms may have appeared.

By this stage the patient may have noted gradually failing vision in one or both eyes. Proteinuria has become constant, and peripheral edema is an annoying manifestation. Hypertensive levels are now persistently obtained when the blood pressure is checked, and slight azotemia is noted. Calcification is found within the arteries of the legs or pelvis by roentgenography; typical diabetic retinopathy, with hemorrhages, soft and hard exudates and early areas of retinitis proliferans, is also found.

Despite now valiant attempts to control the diabetes, severe kidney damage has been established. Renal insufficiency continues to progress, with massive proteinuria leading eventually to hypoproteinemia, anemia and constant azotemia. The terminal weeks or months are characterized by persistent hypertension, uremia and, often, cardiac decompensation and blindness. Not infrequently the insulin requirement falls, and to the observer not acquainted with the history of the patient it may seem that the diabetic condition is mild. Death most frequently takes place in uremia or congestive heart failure, or less commonly from myocardial infarction.

Incidence and Duration of Renal Complications

Both the incidence and the severity of diabetic nephropathy become greater with increasing duration of the diabetic state. Furthermore, the duration of diabetes appears to be of more significance than the age of the patient in the determination of the frequency and extent of renal involvement among patients whose diabetes begins early in life.

The 62 patients found to have impairment of renal function of varying degrees of severity included 29 patients, or 28.1 per cent, of the 103 patients included in the study whose diabetes had been present for twenty to thirty-four years. Similarly, 14 of the 58 patients (24.1 per cent) with diabetes of fifteen to twenty years' duration and 19 of 86 patients (22.1 per cent) who had had diabetes for ten to fifteen years also showed some degree of renal insufficiency. These 62 patients with evidence

of diabetic nephropathy were examined at an average age of 33.3 years after diabetes had been present for an average of 18.1 years. Manifestations of kidney disease had been present for varying periods of time prior to the present examination.

Numerous reports in the literature suggest that intercapillary glomerulosclerosis associated with diabetes occurs most commonly in older patients in the sixth and seventh decades.[3, 4, 11-19] Experience at this clinic, however, indicates that although diabetic nephropathy is seen among middle-aged and older diabetics it occurs with greatest frequency among patients in their thirties and forties who have had severe, poorly controlled diabetes for twenty or more years. It is possible that this occurrence among patients in earlier decades has escaped general attention because of the relatively lower incidence of diabetes itself at younger ages.

The sex distribution of our cases showed no important difference, there being 25 male and 37 female patients with manifestations of renal involvement. Although most previous reports concerning renal disease in diabetic patients have indicated a higher incidence in one or the other of the sexes, definite factors were generally responsible for the unequal distribution. A similar number of males and females were included in the total group of 247 young patients in which these 62 cases of diabetic nephropathy were observed. This equal sex distribution is characteristic of diabetes in early life, as the greater frequency in females does not become manifest until middle age.

Severity of Diabetes

Although admittedly not entirely satisfactory, description of the severity of diabetes in terms of the daily insulin dosage is widely employed. Among these 62 young patients with severe diabetes who showed evidence of renal disease, 57 were taking more than 30 units and 34 more than 50 units daily. Thus, diabetic nephropathy is seen to be a complication among young patients with severe diabetes. This is in striking contrast, however, with the majority of previously reported cases of renal disease complicating diabetes, — cases of intercapillary glomerulosclerosis, — which have been observed in elderly patients with onset of diabetes after the age of forty in whom the disease is generally present in a milder form.[3, 4, 12] The daily requirement for insulin often falls significantly during the terminal stages of this type of renal disease. This progressive decrease in insulin requirement may then cause these patients to seem to have a mild form of diabetes when they are seen only during the late stages of the disease or when the hospital record of the terminal illness is reviewed.

Control

The existence of any correlation between control of diabetes and incidence of complications has been questioned previously by some investigators and definitely denied by others.[13-18] However, our data afford what we regard as convincing evidence that careful, continuous control of diabetes does prevent or delay the onset of this specific renal complication among young diabetic patients. The type of treatment and degree of control of the diabetic state maintained over the years was evaluated for each patient according to previously established standards of control, which included 4 grades: excellent, good, fair and poor.

STANDARDS OF CONTROL

Excellent Control

Patient must never have been in coma.

Insulin was begun within a few weeks of the onset of diabetes.

Urine tests for sugar made more than once daily, continuously since onset of diabetes, with conscientious attempt to have the urine sugar-free or nearly so before meals. Insulin-dosage adjustments determined by results of urine tests.

Diet must have been weighed for at least 80 per cent of the duration since onset of symptoms of diabetes.

Regular physical examination and laboratory tests, made by a physician, must have been faithfully completed at least once annually. Blood and urine tests satisfactory.

Good Control

Patient must never have been in coma except in those instances in which the initial diagnosis of diabetes was made in coma.

Insulin was begun within a few weeks after the onset of diabetes.

Urine tests for sugar made at least once daily, continuously since onset of diabetes, with conscientious attempt to have the urine sugar-free or nearly so before meals. Insulin-dosage adjustments were made according to results of urine tests.

Diet must have been weighed for the first six weeks of treatment and thereafter at intervals, with careful measurement of food at all other times since onset of diabetes.

Regular physical examination and laboratory tests made by a physician at least once annually. Blood and urine tests satisfactory.

Fair Control

Patient must never have been in coma (except for cases in which the diagnosis was made with the patient in coma, or rare cases in which unavoidable overwhelming infection or other complication precipitated coma).

Insulin begun within twenty-four months of onset of symptoms of diabetes.

Tests of the urine for sugar were made with a frequency of one or more times weekly in an attempt to have sugar-free urine tests.

Dietary management by the patient must have been conscientiously attempted, although all food was not weighed or measured. Patient rarely if ever indulged in gross dietary indiscretions.

Satisfactory blood-sugar determination made at the time of physical examinations by the patient's physician at least once every two years.

Poor Control

Avoidable coma one or more times.

Insulin not begun until more than twenty-four months after onset of diabetes and in some cases taken irregularly.

Urine specimens tested infrequently, or at intervals of months or years.

No measurement or weighing of food in relation to urine tests or insulin dosage.

No regular examinations by a physician. At long intervals, office or hospital examination showed marked glycosuria and hyperglycemia.

Among these 62 patients with renal complications, none had exercised better than fair control.

None of the total group of 247 patients who maintained good or excellent control of their diabetes was found to show signs or symptoms of this type of kidney disease, even after twenty to thirty-four years of diabetes.

Forty-nine patients, or 80 per cent of those who showed evidence of renal damage, were found to have maintained poor control. Twenty-six of these patients had, in fact, been in diabetic coma on one or more occasions.

Fatal Cases

Thirteen of these 62 patients died during the year in which the study was conducted. The basic cause of death in all cases was considered to be renal failure. However, the immediate cause of death in one case was myocardial infarction, and in another a cerebral embolus was the terminal event.

The average age at death of these 13 patients was 33.0 years. Diabetes had been present for an average of 18.8 years. The average age at onset of diabetes was 14.2 years. The earliest manifestations of diabetic nephropathy among these fatal cases were noted at the average age of twenty-two years, or eleven years prior to death. The typical findings and their time of appearance or occurrence, in relation to each other and according to duration of diabetes, are summarized in Table 1.

TABLE 1. *Chronologic Data on Significant Events in 13 Fatal Cases of Diabetic Nephropathy.*

Age of patient:	AVERAGES
At onset of diabetes	14.2
At onset of nephropathy	22.0
At death	33.0
Duration of diabetes:	
At onset of proteinuria	13.9
At onset of retinitis	14.4
At onset of hypertension	15.9
At onset of edema	16.8
At onset of congestive failure	17.9
Duration of condition:	
At death from diabetes	18.8
At death from nephropathy	11.0

DISCUSSION

No single symptom or clinical manifestation is diagnostic of diabetic nephropathy. Instead, numerous clinical findings are associated with the progression of this relatively specific type of degenerative renal disease, which is seen among young diabetic patients, and these classically occur in an orderly sequence. The resulting syndrome affords evidence on which a presumptive diagnosis of diabetic nephropathy can easily be made. A positive diagnosis of this condition should be reserved, however, until histopathological examination of the diseased kidneys has been completed.

For many years certain diabetic patients were considered to have disease of the kidney caused by factors unrelated to their diabetes. The patients so regarded were those with signs and symptoms resembling the manifestations seen during the nephrotic phase of chronic glomerulonephritis. Several such patients were the subjects of the initial investigation by Kimmelstiel and Wilson,[1] who demonstrated certain distinctive lesions found among the capillary loops of the renal glomeruli. Since that time numerous observers have emphasized the specificity of these changes for diabetes and have stated that they were not the result of coincidental independent kidney disease. It is now generally agreed that the particular lesions described by Kimmelstiel and Wilson are seen much more frequently among diabetic patients, particularly at older ages, and although they have occasionally been reported they occur only rarely in other diseases.

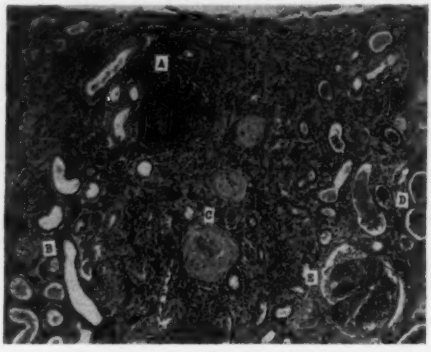

FIGURE 1. *Multiple Lesions Characteristic of Diabetic Nephropathy.*

A = Dense lymphocytic infiltration, suggesting chronic pyelonephritis. B = Hyperplastic arteriolar sclerosis. C = Linear scar with hyalinized glomeruli, probably on vascular basis. D = Tubules containing polymorphonuclear leukocytes and precipitated protein (acute pyelonephritis). E = Glomerulus showing intercapillary glomerulosclerosis and fibrosis of capsule probably due to pyelonephritis. (Hematoxylin and eosin x70.)

Intercapillary glomerulosclerosis is only one of several lesions that are consistently seen at postmortem examination in the kidneys of young patients with poorly controlled diabetes of long duration. It has been observed in the Department of Pathology of this hospital that young diabetic patients who die primarily of renal disease invariably show at autopsy a combined or mixed type of renal disease. The lesions found include those characteristic of some or all, — usually all, — of the following: acute and chronic pyelonephritis, arteriosclerosis, arteriolosclerosis and intercapillary glomerulosclerosis. Evidence of glomerulonephritis is rarely seen. Necrotizing papillitis[17] resulting from

severe focal renal infection was not observed in any of the cases in this group. No young diabetic patient observed in this hospital has been found to have intercapillary glomerulosclerosis as the only lesion demonstrable at autopsy. The characteristic histopathology of diabetic nephropathy is illustrated in Figure 1, which shows the lesions observed in a patient who died at the age of thirty-two and had diabetes for twenty-one years.

This combination of lesions, resulting from infectious, degenerative and perhaps nutritional or endocrine as well as other factors, is not a constant or even a frequent pathological finding in any disease other than diabetes. Any or all of the lesions seen on histopathological examination in young diabetic patients with renal complications may occur as an independent condition and may be seen in cases of kidney disease in nondiabetic patients. However, except for cases of malignant hypertension, the presence of extensive arterial and arteriolar sclerosis is rarely observed in cases of kidney disease occurring in nondiabetic patients under the age of forty.

Summary

A type of renal disease of mixed etiology is described; the term "diabetic nephropathy" is suggested for it. It is seen only among patients with diabetes and, although occurring at all ages, it is seen most frequently among young patients in their thirties and forties with severe, poorly controlled diabetes of long duration.

The chronologic development of the clinical manifestations of diabetic nephropathy include albuminuria, increased index of capillary fragility, retinal hemorrhages, peripheral edema, hypertension and azotemia, all progressing to death most commonly in uremia but at times as the result of myocardial infarction, congestive heart failure or cerebrovascular accident.

Histopathological findings characteristic of diabetic nephropathy consist of a combination of lesions including all or most of the following: acute and chronic pyelonephritis, arteriosclerosis, arteriolosclerosis and intercapillary glomerulosclerosis.

Manifestations of diabetic nephropathy were shown by 62 patients (25 per cent) among a group of 247 young patients with severe diabetes of ten to thirty-four years' duration with onset at ages between eighteen months and thirty years.

Among the total group of 247 patients there were 37 who had adequately controlled their diabetes (excellent or good control) by attention to a program that included early and continued use of insulin, careful measurement of a planned diet, regular medical examination and daily urine tests with adjustment of diet and insulin to secure sugar-free specimens. *Not one of these had developed nephropathy at the time of the study.*

A keener awareness of the existence of this syndrome as a clinical entity would result in better appreciation of its severity and in wider recognition of the importance of the control of diabetes in the prevention of its development.

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AMELIORATION OF DIABETES AND STRIKING RARITY OF ACIDOSIS IN PATIENTS WITH KIMMELSTIEL-WILSON LESIONS*

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A REMARKABLE reduction in insulin requirement in a patient (Case 1 — H. R.) with diabetes, who died in uremia, focused attention on the general subject of occasional spontaneous amelioration in diabetes mellitus. Improvement in diabetes has been described as coincident with the following: limitation of diet and consequent loss of weight,[1] cirrhosis,[2] myxedema,[3] extirpation of pheochromocytoma,[4] radiation of the pituitary gland in acromegaly,[5] onset of Addison's disease,[6] relief of Cushing's syndrome,[6] senescence,[7] and also, most dramatically, in anterior-pituitary-artery thrombosis. None of these mechanisms seemed to be operative in Patient H. R., in whom the dominant feature of her later years was renal insufficiency.

The clinical axiom that progression of renal disease may mitigate diabetic severity has long been circulated, but references to this phenomenon in the literature are rare and sparsely documented. An early observation appears to have been made by Stokvis,[8] who in 1886 referred to instances of modification of diabetes in the presence of albuminuric nephritis. In 1905 Carl von Noorden[9] re-emphasized that the disappearance of diabetic glycosuria with onset of kidney impairment was widely recognized by clinicians.

In view of these observations it was decided to undertake a study of the incidence and degree of improvement in diabetes mellitus with renal disease and to review the histories of all patients with diabetes who were autopsied at the Johns Hopkins Hospital for the thirteen-year period 1938-1950.¶

This afforded an opportunity to compare the course of diabetes mellitus in patients with and without renal lesions.

CASE REPORTS

Striking Improvement in a Patient with Diabetes Mellitus and Kimmelstiel-Wilson Lesions

CASE 1. H. R. (JHH 247064), a Negro woman, developed diabetes mellitus in 1939 and died in 1950 at the age of 67. Her mother and two sisters had diabetes. The patient weighed 250 lb. at the onset of her disease, 200 lb. in 1943, 225 lb. in 1944 and 237 lb. in 1949. She was first seen at the hospital in 1941; her blood sugar was 300 mg. per 100 cc. at that time. She had been taking 60 units of insulin daily. She made only a few visits to the clinic and her diabetes was never regulated. In 1943 she was admitted to the gynecological service for hysterectomy. Her blood pressure at that time was 136/86. Laboratory examination of the urine showed no albumin and ++ sugar. Examination of the blood revealed a fasting sugar of 292 mg. and a nonprotein nitrogen of 45 mg. per 100 cc. After operation she was put on a regimen of: protein, 70 gm., fat, 70 gm. and carbohydrate, 120 gm., and 95 units of insulin daily. No infection was present during this regulation. Her fasting blood sugar at the time of discharge was 256 mg. per 100 cc.

She did not return until 1945, when she was readmitted because of an infected toe. She had taken 55 to 80 units of insulin daily in the interval between admissions. At physical examination gangrene of one toe was seen. The blood pressure was 154/80. Laboratory examination of the urine revealed ++++ sugar and no albumin. Examination of the blood showed a fasting sugar of 310 mg. and a nonprotein nitrogen of 30 mg. per 100 cc. She was put on a regimen of: protein, 70 gm., fat, 70 gm. and carbohydrate, 120 gm., and 85 units of insulin daily. The toe was amputated, and the diabetes became better controlled, with a fasting blood sugar of 156 mg. per 100 cc. on 75 units of insulin daily. The weight was 205 lb.

In 1945 a second gangrenous toe was removed at another hospital. The patient was taking 90 units of insulin daily. She did not adhere to any diet in the period 1946–1949 and gradually reduced her insulin intake to 40 units daily. She developed severe attacks of weakness, and a physician told her that she was taking too much insulin.

In May, 1949, she developed marked swelling of the ankles and exertional dyspnea. She was seen on the out-patient service. Examination showed drowsiness, a blood pressure of 170/92 and marked edema of the legs. Cataracts were present, and the fundi could not be seen. Laboratory examination of the urine showed no sugar and ++ albumin. Examination of the blood revealed a fasting sugar of 200 mg. and a nonprotein nitrogen of 115 mg. per 100 cc. She was admitted to the hospital for study in September, 1949, having stopped taking insulin in June, 1949. Physical examination showed a weight of 246 lb., edema of the ankles, a blood pressure of 200/100 and evidence of mild cardiac failure. Laboratory examination of the urine showed ++ albumin and + sugar. Examination of the blood revealed a fasting sugar of 158 mg., a nonprotein nitrogen of 80 to 125 mg. and a cholesterol of 309 mg. per 100 cc.; the albumin was 3.7 mg. and the globulin 2.3 mg. per 100 cc. The basal metabolic rate was +6 per cent; a phenolsulfonphthalein test returned 2 per cent in 2 hours. After the intravenous injection of 6.5 units of crystalline insulin the fasting blood sugar was 260 mg. per 100 cc., 228 mg. at 20 minutes, 215 mg. at 30 minutes, 220 mg. at 45 minutes, 220 mg. at 60 minutes and 208 mg. per 100 cc. at 90 minutes. The 24-hour urinary excretion of 17-ketosteroids was normal, and x-ray films of the skull showed a normal sella turcica. The cephalin-flocculation test was negative at 48 hours. The patient was digitalized and put on a diet of: protein 70 gm., fat 60 gm. and carbohydrate 120 gm., with 4.0 gm. of salt. The fasting blood sugar gradually rose to 378 mg. per 100 cc. while she was not on insulin, and she was then given 10 units of insulin daily. The fasting blood sugar fell to 120 mg. on this regimen.

After discharge the patient never returned to the clinic. On March 8, 1950, she died, apparently of uremia, and the body was returned to the hospital for autopsy. She had had no ketosis or coma, and the urine was negative for acetone and diacetic acid on the basis of more than 75 specimens examined. Autopsy showed severe Kimmelstiel-Wilson lesions of the glomeruli and severe arteriolonephrosclerosis. The anterior pituitary gland was normal.

Repeated Acidosis and Lack of Improvement in Diabetes in a Patient with Severe Vascular Nephritis and Uremia

CASE 2. E.D. (JHH 525254) was 32 years of age when first seen at this hospital. His mother, father and maternal aunt had diabetes mellitus. The patient was discovered to have diabetes mellitus in 1930, at the age of 12. His physician at first gave him 70 units of insulin daily, but the patient

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¶This includes the first four months of 1951.

had an episode of shock and was then regulated on 30 to 50 units daily. In 1932 he stopped insulin on the advice of a physician and was shortly thereafter hospitalized in diabetic coma. He was again regulated on 50 units of insulin daily. He remained fairly well regulated on this dosage until admission, except for an episode of severe acidosis during an infection. His exact diet during these years is unknown; his average weight in adult life was 140 to 145 lb.

Six years before admission the patient developed sudden blindness in his right eye; vision then gradually returned. This occurred again 2 years before entry, but clearing was incomplete. Three months before admission, after sustaining a trauma, he became blind in the right eye; an ophthalmologist told him that he had a detached retina and high blood pressure. There had also been some dimness of vision in the left eye. He was then examined by an internist and told that his blood pressure was 230 and that he had albuminuria and kidney disease. There was no history of acute nephritis, although he had scarlet fever in childhood. There had been no ankle swelling, dyspnea or orthopnea. He had had numbness in the feet for 2 years before admission. On examination he weighed 148 lb. His blood pressure was 220/130. He did not appear ill. No edema or dyspnea was noted. The right vitreous was hazy. The left eye showed edema of the retina and disk. There were retinal hemorrhages and exudates. The arteries were extremely small. The lungs were clear and the heart was not enlarged. The deep reflexes in the legs were absent, and the vibratory sensibility of the right leg was diminished. Laboratory examination of the urine revealed no sugar, a + to +++ albumin and rare red blood cells and hyaline casts; acetone and diacetic acid were negative. Examination of the blood disclosed a fasting sugar of 500 mg., a nonprotein nitrogen of 69 to 80 mg., and a serum cholesterol of 350 mg. per 100 cc.; the total serum protein was 6.5; the serum albumin was 4.1 and the serum globulin 2.3 mg. per 100 cc. The carbon-dioxide combining power of the blood was 20.8 milliequiv. per liter. A phenolsulfonphthalein test returned 12 per cent in 2 hours in 245 cc. One examination of the urine showed no doubly refractile bodies. The patient was placed on a diet of protein 90 gm., fat 100 gm. and carbohydrate 200 gm., with 2.0 gm. of salt and 70 units of insulin daily. He soon had hypoglycemia, and a reduction in dosage to 50 units per day resulted in a fasting blood sugar of 116 mg. per 100 cc.

In March, 1950, when he was seen by his private physician, his blood pressure was 190/110. There was no edema. The fasting blood sugar was 378 mg. and the nonprotein nitrogen 96 mg. per 100 cc. He was told to remain on 50 units of insulin daily.

In September, 1950, he was readmitted to the hospital in a semicomatose state. Three days before admission he developed oliguria and, for the first time, edema; this involved the face as well as the extremities. The blood pressure was 225/130. The patient was acutely ill and semistuporous. Anasarca was present and the heart was enlarged. Laboratory examination of the urine showed +++ sugar and no albumin on admission; subsequent examination showed a ++++ sugar, no acetone and + albumin, with 10 to 25 red blood cells and many granular casts per high-power field. Examination of the blood disclosed a fasting sugar of 468 mg. per 100 cc., a carbon-dioxide combining power of 17.0 milliequiv. per liter and a nonprotein nitrogen of 156 mg. per 100 cc. The serum albumin was 2.9, the globulin 1.2 and the calcium 6.4 mg. per 100 cc.; the potassium was 3.4 milliequiv. per liter. The patient was given glucose and calcium gluconate intravenously. The nonprotein nitrogen rose to 214 mg. per 100 cc. The patient was also given 30 to 40 units of insulin daily, but the fasting blood sugar remained above 300 mg. per 100 cc. He died in pulmonary edema on September 18, 1950. The diagnosis at autopsy was severe arteriolonephrosclerosis.

The Exceptional Case of Acidosis in a Patient with Severe Kimmelstiel–Wilson Lesions

Case 3. M. J. (JHH 339854), a Negro woman, when first seen in 1932 was 48 years old and weighed 130 lb. Her highest weight had been 148 lb. in 1930. There was no family history of diabetes mellitus. In 1932 she was found to have glycosuria and a fasting blood sugar of 265 mg. per 100 cc. Her blood pressure was 190/90; there was no albuminuria. She was given a diet of protein 70 gm., fat 100 gm. and carbohydrate 100 gm. daily, but did not follow it and had a blood-sugar concentration above 300 mg. per 100 cc., with ++++ glycosuria. In 1939 she was given a diet of protein 70 gm., fat 100 gm. and carbohydrate 100 gm., together with 20 units of insulin. Her weight at that time was 110 lb. The dosage of insulin was increased until she was taking 65 units daily, but on this dosage she still had ++++ glycosuria. Despite blood-sugar concentrations as high as 468 mg., no acetone or diacetic acid was revealed in the urine in more than 50 examinations made from 1932 to 1943.

The patient was at all times unco-operative and failed to adhere to her diet. No data are available on albuminuria or blood pressure in the years 1932–1944. Her last visit to the clinic was on September 7, 1943. At that time ++++ glycosuria was noted and she was told to take 60 units of insulin daily.

On December 18, 1944, she was admitted to the hospital in coma. She had suffered from an infected toe for the preceding 6 months, and 3 weeks before admission she became orthopneic and her physician told the family that she had pneumonia. Four days previously her insulin supply had run out. She gradually lapsed into coma. At examination her blood pressure was 134/66. She was in coma, dehydrated and breathing deeply and regularly. One toe was gangrenous. There was minimal edema of the legs and thighs. Cataracts were present, and the fundi could not be seen. Laboratory examination of the urine showed ++++ sugar, acetone and diacetic acid and a ++ albumin. Examination of the blood disclosed a sugar of 510 mg. per 100 cc. and a carbon-dioxide combining power of 12.4 milliequiv. per liter; the nonprotein nitrogen was 48 mg. per 100 cc. and the chloride 107.5 milliequiv. per liter. She was given large doses of regular insulin (460 units in the first 24 hours) and intravenously administered saline solution, plasma and sodium lactate. Twelve hours after admission the blood sugar was 420 mg., the carbon-dioxide combining power was 16.6 milliequiv. per liter and the urine contained ++++ acetone and diacetic acid. Sixteen hours after admission the carbon-dioxide combining power was 21.6 milliequiv. per liter, but the urine still contained diacetic acid. Twenty-four hours after admission the urine acetone and diacetic were + and the carbon-dioxide combining power was 28.4 milliequiv. per liter. The blood pressure was 142/64. Numerous extrasystoles appeared. Thirty-six hours after admission the patient was conscious and able to respond to questioning but very dyspneic. Numerous rales appeared in the chest. While receiving an infusion of a 50 per cent solution of glucose she died abruptly of respiratory failure. Her diabetes had apparently been adequately controlled, since the last urine specimen obtained before death showed +++ sugar and no acetone or diacetic acid.

Autopsy showed a large fresh myocardial infarction. The kidneys showed moderately severe +++ Kimmelstiel-Wilson lesions and severe arteriolosclerosis. The anterior pituitary gland was normal.

A Patient with Diabetes and Kimmelstiel–Wilson Lesions Dying in Hypoglycemic Shock from the Same Insulin Dosage Previously Required for Maintenance

Case 4. C. G. (JHH 372661), a Negro woman, was followed from 1927 until her death in 1951 at the age of 58. One sister had diabetes. The patient's highest weight was 173 lb. in 1927; in 1930, when her diabetes was discovered, she weighed 163 lb. Her weight slowly fell, so that in 1945 she weighed 155 lb., in 1948 148 lb. and in 1949 118 lb. In 1930 it was noted that her urine sugar was ++++; a fasting blood sugar in 1933 was 350 mg. per 100 cc. She was placed on a diet of protein 60 gm., fat 130 gm. and carbohydrate 80 gm. but continued to have glycosuria. In 1939 she was given a diet of protein 60 gm., fat 60 gm. and carbohydrate 140 gm., with 22 units of insulin. The blood sugar at this time was 254 mg. In 1943 her insulin intake was increased to 32 units daily, but the blood sugar remained at 340 mg. The diet was increased to protein 80 gm., fat 50 gm. and carbohydrate 150 gm. in 1949, but the insulin intake was kept at 32 units daily until admission. Glycosuria disappeared for the first time in 1949, and in 1950 the fasting blood sugar was 130 mg. In 1950 the patient voluntarily discontinued insulin for a week, and glycosuria reappeared. She has never been in coma or acidosis, and more than 50 urine specimens have shown no acetone or diacetic acid.

The patient had a blood pressure of 140/80 in 1927 and 200/110 in 1942 and 1951. Albuminuria was + in 1927 and ++++ in 1947. In 1942 she developed numbness in her legs, and deep tendon reflexes in legs were noted to be absent.

Ophthalmoscopic examination was negative in 1930 but showed many exudates and microaneurysms in 1950.

One year before death she developed swelling of the ankles; this progressively increased despite salt restriction and digitalization. In 1950 she had massive anasarca and was admitted on March 29, 1951, to the medical service. Examination showed marked edema. The blood pressure was 200/110. The heart was enlarged, and there were a few basilar rales. Laboratory examination of the urine revealed no sugar and +++ albumin. On examination of the blood the nonprotein nitrogen was 75 mg. per 100 cc., and fasting blood sugars were 108 mg. per 100 cc. on two occasions. Various treatments for the edema failed to produce a diuresis. The patient's diet was protein 70 gm., fat 50 gm. and carbohydrate 150 gm., and she was given 30 units of insulin daily. On April 7 she was noted to be lethargic, and she complained of precordial pain. She received no insulin after the morning of April 7. On April 8 she was found unconscious, but shortly became responsive after intravenous injection of glucose. On April 9 she again lost consciousness, responding immediately to intravenous injection of glucose. On April 10 and 11 she had a number of similar attacks, despite the addition of 500 cc. of orange juice to her diet. On the morning of April 12 she became unconscious, responding somewhat to intravenous injection of a 50 per cent solution of glucose, but by evening she began to sweat profusely, went into shock and died. No glycosuria had been disclosed at 20 examinations in spite of liberal oral and intravenous administration of glucose. Data on blood sugar noted during the episodes described above unfortunately were lost. At autopsy the kidneys showed marked Kimmelstiel–Wilson lesions, with moderately extensive arteriolonephrosclerosis. The pituitary and adrenal glands were normal.

Marked Reduction in Insulin Requirement in a Case Recently Studied but Not Included in the Tables

Case 5. H. F. (JHH 122151), a Negro woman, was first seen at the hospital in the Obstetrical Clinic in July, 1904. At that time no albumin or sugar was noted in the urine. There was no family history of diabetes mellitus. In 1921 the patient developed urinary burning, and on the basis of persistent positive urine cultures showing *E. coli* a diagnosis of chronic pyelonephritis was made. In 1921 the blood pressure was 118/78, in 1937 120/70 and in 1938 145/100. Her weight was 161 lb. in 1921; this changed only slightly in succeeding years.

Diabetes mellitus was discovered in 1937, and insulin therapy was started in 1938. The accompanying chart shows the patient's insulin requirement, weight and fasting blood sugars from 1938 through 1951. She has never been in diabetic acidosis or coma, and more than one hundred urine specimens have failed to show acetone or diacetic acid. During this time the diet was relatively constant, comprising protein 65 gm., fat 40 gm. and carbohydrate 100 gm. daily. She was free of infection at the times when these figures were recorded.

Date	Weight	Insulin	Fasting Blood Sugar
	kg.	*units/day*	*mg./100 cc.*
1937	80	0	243
1940	78	29	340
1945	71	72	108
1949	72	82	245
1950 (March)	72	0	194
1950 (June)	62	0	64
1951	52	0	70–127

The albuminuria was first noted in 1950, when it was +++, and it continued to the time of death. The urine had been free of albumin in 1945. In March, 1950, the patient developed exertional dyspnea and was admitted to the medical service. Examination showed a blood pressure of 270/115, marked cardiac enlargement and rales at the lung bases but only slight pretibial edema. Laboratory examination of the urine showed no sugar, a +++ albumin and many hyaline and granular casts. Examination of the blood revealed a sugar of 158 mg., a nonprotein nitrogen of 125 mg. and a cholesterol of 295 mg. per 100 cc. A phenolsulfonphthalein test returned 55 per cent in 2 hours. The patient was digitalized and given a low-salt diet, and the blood nonprotein nitrogen slowly fell to 49 mg. Insulin was discontinued, and the highest fasting blood sugar was 194 mg. She was then followed in the clinic and became progressively edematous. For a time the edema was controlled by mercurial diuretics. Further laboratory findings in the clinic showed a normal sella turcica on x-ray films of the skull and an Addis count of 183,315 casts, 19,309,108 red blood cells and 105,008,943 white blood cells, in a 12-hour specimen on one occasion, and 303,025 casts, 29,211,634 red blood cells and 61,635,336 white blood cells in a second 12-hour specimen. On 6 occasions microscopical examination of the urine with polarizing lenses was negative for doubly refractile casts. A glucose-tolerance test made after ingestion of 100 gm. of glucose by mouth (small amount of vomitus one hour after test started) showed a fasting blood sugar of 104 mg., 227 mg. in 1 hour and 136 mg. in 2½ hours. On April 5, 1951, the patient developed a stroke; she was admitted to the Baltimore City Hospital on April 20. No insulin was administered during her hospitalization, and 5 determinations of the fasting blood sugar were 79, 76, 66, 81 and 82. mg. per 100 cc. A glucose-tolerance test (with 50 gm. of glucose taken by mouth) gave the following blood-sugar concentrations: fasting, 80 mg., 171 mg. at 1 hour; 173 mg. at 2 hours; and 151 mg. at 3 hours. After the intravenous administration of 5 units of crystalline insulin the following determinations were obtained: fasting blood sugar, 78 mg.; 68 mg. at 10 minutes; 55 mg. at 20 minutes; 55 mg. at 30 minutes; 48 mg. at 45 minutes; and 55 mg. at 65 minutes. The nonprotein nitrogen gradually rose from 78 mg. on admission to 166 mg. per 100 cc. at the time of death.

Autopsy showed extensive Kimmelstiel–Wilson lesions of the kidneys, with marked arteriolonephrosclerosis. There was no pyelonephritis. The pituitary gland was normal.

Methods

During the study period 7145 autopsies were performed; a history of diabetes mellitus was recorded in 178. The clinical records of each of the 178 patients were reviewed in terms of the course of the diabetes and renal disease. These data were correlated at first with the renal lesions recorded in the autopsy reports. There seemed to be a difference between the course of diabetes in patients with and without Kimmelstiel–Wilson lesions, and it was decided to make a study of the course of diabetes in patients with Kimmelstiel–Wilson lesions; in patients with renal lesions of other types; and in patients with no evidence of renal disease at autopsy.

To ensure uniform interpretation in terms of current diagnostic concepts of the Kimmelstiel–Wilson lesion,[10, 11] the kidney sections were reappraised. The sections selected for review were all those in which the protocols suggested the possibility of Kimmelstiel–Wilson lesions. This included all patients diagnosed in the autopsy reports as demonstrating Kimmelstiel–Wilson lesions, as well as the majority of those showing other renal lesions. All slides were viewed by the pathologist, who had not participated in the clinical study and had no knowledge of the patient's course; his diagnosis was accepted as final.

In addition to the comparative study, a search was made for patients showing Kimmelstiel–Wilson lesions who had been autopsied at the Johns Hopkins Hospital prior to 1938. Those patients were selected for review who had a history of diabetes and any renal lesion suggesting the Kimmelstiel–Wilson glomerular change. It was found that the kidney sections made prior to 1925 were not satis-

factory for this study. Only eight patients showing Kimmelstiel–Wilson lesions were found during the period 1925–1937; these are recorded separately. The course of their diabetes has not been compared with that of control groups selected from the same period of time.

The decision concerning improvement in the diabetic status is difficult in view of the influence of diet, weight loss, infection and the attitude of the physician toward regulation of the diabetes. It was believed that a true evaluation could be made by the estimation of insulin dosage, weight change and fasting blood sugars at basal and preterminal points of the diabetic history, when the patient was relatively free of infection and gangrene. Furthermore, the inclusion in the study of all patients with diabetes autopsied during the thirteen-year period was regarded as affording unselected control groups. Since the patients in all groups were treated for their diabetes in the same hospital during the same era, it was concluded that unmeasurable variables would be balanced at least partially for the three groups. The relation of diet to improvement is not discussed in this report, as dietetic histories are often inaccurate. Examination of the recorded diet figures showed no trend for any of the groups. When more than one determination of blood-sugar concentration were available, these figures were averaged.

The basal period was in most cases chosen from the middle third of the diabetic course — a time when the patient was free of infection, gangrene and myocardial infarction. The preterminal period was chosen as that time nearest to death of the patient at which there was adequate information and freedom from tissue necrosis. Values obtained during acute stress have been avoided whenever possible, although in some cases there were few data except concerning the terminal event. In such cases the terminal data were used. In summary, then, the decision on improvement or nonimprovement was based on a comparison of the insulin requirement in the basal and preterminal periods.

When the data for the three groups had been tabulated, it was apparent that a more precise study could be obtained by eliminating certain cases. Since there has been controversy[11, 12] concerning the specificity of mild Kimmelstiel–Wilson lesions, it was decided not to include in Tables 2 to 6 the patients who showed only mild Kimmelstiel–Wilson lesions. In addition, patients whose duration of diabetes was less than three years are not shown in Tables 2 to 6; thus only cases providing more adequate observation periods are listed.

The diagnosis of diabetic acidosis likewise presents problems. One-plus positive tests for acetonuria and diacetic aciduria have not been used. Acetonuria occurs as a result of starvation and cannot be relied on as evidence of diabetic acidosis without corroboration. Finally, lowering of the carbon-dioxide combining power of the blood is frequently caused by other factors and cannot be employed as a measure of diabetic acidosis unless acetonuria and diacetic aciduria are present, together with fairly high blood-glucose concentrations. Hence, the term "acidosis," as used in this paper, means the presence of acetone and diacetic acid in the urine together with high blood sugar and lowered blood carbon-dioxide combining power. The criteria for mild, moderate and severe ketosis are those in common use.[1]

The criterion used for the Kimmelstiel–Wilson lesion[11] in this report is solely the "lumpy-loop" or hyaline mass in the glomerulus. This lesion is associated uniquely with diabetes mellitus. The term "intercapillary glomerulosclerosis" has been avoided partly because of its possible confusion with an entirely separate pathological entity, intercapillary glomerulonephritis, and partly because of some doubt concerning the intercapillary location of the hyaline mass. Varying degrees of arteriolosclerosis and arteriosclerosis of the kidney are almost always associated with the Kimmelstiel–Wilson lesion. If these latter processes are marked, the identification of the hyaline masses may be difficult. A review of the pituitary sections available in over 80 per cent of the Kimmelstiel–Wilson cases revealed no uniformly significant pathologic change. No special technics[13] were employed in searching for vascular lesions of the anterior pituitary. In addition, protocol statements concerning sections of the liver and thyroid and adrenal glands indicated no consistent abnormality of these organs.

TABLE 1. *Severity of Diabetes in 57 Patients with Kimmelstiel–Wilson Lesions (1925–1950) and 133 Patients with Diabetes Mellitus (1938–1950).*

	With Kimmelstiel–Wilson Lesions	With Other Renal Lesions	With No Renal Lesion
No. of patients	57	48	85
Color (white)	29	33	44
(Negro)	28	15	41
Sex (male)	16	15	40
(female)	41	33	45
Average age at death	57	60	50
Insulin requirement (Average no. of units per day)			
Basal*	24	18	15
Preterminal	15	52	47
History of acidosis	2 (4%)	20 (42%)	45 (53%)
Death in coma	0	8 (17%)	17 (20%)

*In these tables the word "basal" is defined as the period of the diabetic course when it is uncomplicated and in its middle years. The word "preterminal" is defined generally as that period of the diabetic course prior to the final illness and its stress.

RESULTS

In Table 1 are presented the data on severity of diabetes in all patients studied. The average basal insulin requirements of the three groups indicate that during the midphase the diabetes of patients with Kimmelstiel–Wilson lesions was fully as severe as that of the control groups. At the end of life the

diabetes of the Kimmelstiel–Wilson group was significantly less severe than the diabetes of the controls. Moreover, whereas on the average the insulin requirement of the Kimmelstiel–Wilson group diminished over the years, that of the control groups more than doubled. The rarity of acidosis in the

of 20 units or less occurring in 63 per cent of the Kimmelstiel–Wilson group, in 59 per cent of those with other renal diseases and in 64 per cent of those with no renal lesions. In the preterminal period, however, a striking change has occurred; an insulin requirement of 20 units or less is now found in 83

TABLE 2. *Changes in Insulin Requirement in 114 Selected Patients* with Diabetes Mellitus.*

		With Kimmelstiel–Wilson Lesions				With Other Renal Lesions		With No Renal Lesion	
		1925–1937	1938–1950	TOTAL					
		no.	no.	no.	%	no.	%	no.	%
No. of patients		8	33	41		29		44	
No. of patients classified according to range of insulin requirement:									
0 units per day	B†	5	16	21	51	13	45	15	34
	P‡	5	22	27	66	4	14	4	9
1–20 units per day	B	0	6	6	12	4	14	13	30
	P	1	6	7	17	4	14	6	13
21–40 units per day	B	3	5	8	19	5	17	12	27
	P	2	3	5	14	6	21	14	32
41–60 units per day	B	0	4	4	10	4	14	2	5
	P	0	2	2	5	7	24	11	25
> 60 units per day	B	0	2	2	5	3	10	2	5
	P	0	0	0	0	8	28	9	21

*The term "selected patient" signifies one in whom the duration of the diabetes has been at least three years. In addition, if it is a patient with Kimmelstiel–Wilson lesions the pathologic change must be of moderate to severe degree.
†Basal period.
‡Preterminal period.

Kimmelstiel–Wilson group is contrasted with its common occurrence in the controls.

Tables 2, 3 and 4 may be considered together, as they cover the same period of time; thus their data on insulin requirement, blood-sugar concentration and weight change are complementary. In these

per cent of the Kimmelstiel–Wilson patients contrasted with 28 per cent of those with renal lesions and 22 per cent of those with no renal lesions.

In Table 3 are assembled data on blood-sugar concentrations. The lowered insulin requirement in the Kimmelstiel–Wilson group cannot be ex-

TABLE 3. *Comparison of Basal and Preterminal Fasting Blood-Sugar Concentrations* in 111 Selected Patients with Diabetes Mellitus.*

		With Kimmelstiel–Wilson Lesions				With Other Renal Lesions		With No Renal Lesion	
		1925–1937	1938–1950	TOTAL†					
		no.	no.	no.	%	no.	%	no.	%
No. of patients		8	30	38		29		44	
No. of patients classified according to range of blood-sugar concentrations:									
< 80 mg. per 100 cc.	B‡	0	0	0	0	0	0	0	0
	P§	2	4	6	16	0	0	0	0
80–120 mg. per 100 cc.	B	0	3	3	8	3	11	4	9
	P	4	7	11	30	2	7	3	7
120–200 mg. per 100 cc.	B	1	4	5	13	9	31	15	35
	P	0	8	8	21	6	21	6	14
200–400 mg. per 100 cc.	B	7	18	25	65	16	55	24	54
	P	1	9	10	26	17	58	22	50
> 400 mg. per 100 cc.	B	0	5	5	13	1	3	1	2
	P	1	2	3	8	4	13	13	30

*Corresponding in time to insulin dosages of Table 2.
†In three patients with Kimmelstiel–Wilson lesions, blood-sugar concentrations were never obtained.
‡Basal period.
§Preterminal period.

three tables, patients whose diabetes was of less than three years' duration and those with minimal Kimmelstiel–Wilson lesions have been excluded. Analysis of the insulin-requirement data (Table 2) shows that during the basal period the ranges of insulin need were the same for all — a requirement

plained by higher fasting blood sugars in association with the lowered insulin dosage. Indeed, the preterminal fasting blood sugars in the patients with Kimmelstiel–Wilson lesions were below 120 mg. per 100 cc. in 46 per cent, whereas normoglycemia was uncommon in the controls. It should be noted

also that 16 per cent of the Kimmelstiel–Wilson patients had preterminal blood-sugar concentrations below 80 mg. per 100 cc.

Table 4 contains data on weight loss during the observation period; these indicate that the proportion of patients losing weight was similar for all groups.

TABLE 4. *Extent of Loss of Weight in 111 Selected Patients with Diabetes Mellitus.*

	WITH KIMMELSTIEL–WILSON LESIONS			WITH OTHER RENAL LESIONS	WITH NO RENAL LESION
	1925–1937	1938–1950	TOTAL		
No. of patients	8	30	38	29	44
No. of patients classified according to range of weight loss*					
0 –10%	2	16	18	9	19
11%–20%	3	7	10	9	12
> –21%	3	7	10	11	13
No. and percentage of patients with significant weight loss			20 (53%)	20 (68%)	25 (57%)

*Percentage of body weight lost during course of diabetes, corresponding in time to observation periods of Tables 1 and 2.

Table 5 includes data on the incidence and severity of diabetic acidosis in the three groups. Only one patient in the selected Kimmelstiel–Wilson group developed diabetic acidosis, whereas this complication occurred in 38 per cent and 51 per cent of the two control groups. In addition, as shown in Table 1, one other patient developed ketosis. This was a patient with mild Kimmelstiel–Wilson lesions who is not shown in the selected group. The acidosis in both patients developed terminally, and neither patient had a previous history of ketosis. The remaining 55 patients had no evidence of acidosis at any time during their diabetes.

Table 6 contains no new data but is presented as a summary of the interpretation derived from Tables 2, 3 and 4. It is concluded that diminishing severity of diabetes mellitus with coexistent renal disease indicates the presence of Kimmelstiel–Wilson lesions in the majority of cases.

TABLE 5. *Incidence of Acidosis and Diabetic Coma in 114 Selected Patients.*

	WITH KIMMELSTIEL–WILSON LESIONS			WITH OTHER RENAL LESIONS	WITH NO RENAL LESION
	1925–1937	1938–1950	TOTAL		
No. of patients	8	33	41	29	44
No. of patients classified according to range of severity of acidosis*:					
None	8	32	40 (98%)	18 (62%)	21 (49%)
Mild	0	0	0	3	4
Moderate	0	0	0	4	4
Severe	0	1	1 (2.5%)	4 (14%)	15 (34%)
No. of patients with acidosis	0 (0%)	1 (3%)	1 (2.5%)	11 (38%)	23 (51%)
No. of deaths in coma	0	0	0	3	5

*Criteria taken from Loeb.[1]

Acidosis in terms of carbon-dioxide combining power of the blood: mild, 21–17 milliequiv. per liter; moderate, 17–11 milliequiv. per liter; severe, < 11 milliequiv. per liter.

If patient is uremic, must have coexistent fasting blood sugar above 300 mg. per 100 cc., and acetone and diacetic acid in urine.

Table 6 contains no new data but is presented as a summary of the interpretation derived from Tables 2, 3 and 4. It is concluded that diminishing severity of diabetes mellitus with coexistent renal disease indicates the presence of Kimmelstiel–Wilson lesions in the majority of cases.

DISCUSSION

It is said that the Kimmelstiel–Wilson clinical syndrome of edema, albuminuria and hypertension occurs characteristically in patients with mild diabetes.[14] The present study is concerned not with the clinical syndrome but solely with the Kimmelstiel–Wilson lesion as a histopathological entity. Observations on the other clinical features of the three groups of patients will be published at a later date.[15]

Appraisal of the severity of diabetes in patients is often based on consideration of the preterminal phase only. Conclusions about mildness of diabetes must be based on the status of severity for the duration of the diabetes. The designation "mild diabetes" includes two elements: a low insulin-dosage requirement and an absence of ketosis. In the middle of the course of diabetes the average insulin requirement of the Kimmelstiel–Wilson group was at least as high as that of the controls. The insulin requirement of the Kimmelstiel–Wilson

TABLE 6. *Estimated Severity of Diabetes in 114 Selected Patients.*

	WITH KIMMELSTIEL–WILSON LESIONS	WITH OTHER RENAL LESIONS	WITH NO RENAL LESION
No. and percentage of patients:			
Better	23 (56%)	2 (7%)	0
Same	14 (34%)	11 (38%)	12 (27%)
Worse	1 (2.5%)	16 (55%)	32 (73%)
Diabetes probable though not demonstrated	3 (7%)		
Totals	41	29	44

group was small in the closing years of the disease. In terms of preterminal insulin requirement, the diabetes of the Kimmelstiel–Wilson group was mild only because amelioration had occurred.

It is difficult to be certain that a lowered insulin dosage is a reflection of improvement, because of the many variables influencing insulin requirement. The tables contain data that indicate that the significantly lowered insulin requirement of the Kimmelstiel–Wilson group cannot be explained by greater weight loss or by less adequate regulation of the diabetes, since the control groups showed equally large preterminal weight loss and had higher fasting blood-sugar concentrations. The use of the two control groups has in part eliminated the influence of the unmeasurable variables. It is concluded that the lowered insulin requirement of the Kimmelstiel–Wilson group can be explained only by improvement of the diabetes. There was no improvement in the diabetes of patients whose renal lesion had not been associated with the characteristic hyaline masses in the glomeruli. Case 2 (E. D.) is an example of unimproved diabetes with severe renal disease without Kimmelstiel–Wilson lesions. In retrospect, it seems likely that the improvement in diabetes in renal disease described by Stokvis[8] and von Noorden[9] occurred in patients with Kimmelstiel–Wilson lesions. McManus[16] in 1949 reported a case of Kimmelstiel–Wilson syndrome with disappearance of hyperglycemia and was the first to comment specifically on the relation of amelioration to this syndrome.

Marked improvement does not occur in every patient with diabetes and Kimmelstiel–Wilson lesions. It is rare, however, for patient in the Kimmelstiel–Wilson group to require an increase of insulin dosage. An example of such an exception is reported (Case 3). Cases have occasionally been found that showed substantial improvement (Cases 1 and 5). The amelioration may be of such degree that the amount of insulin that was previously inadequate to control hyperglycemia can give rise to severe preterminal hypoglycemia (Case 4). Spontaneous hypoglycemia or complete disappearance of diabetes mellitus was not encountered in this series. The phenomenon of improvement with Kimmelstiel–Wilson lesions may explain cases formerly ascribed to other mechanisms, — as in a case reported to show amelioration due to myxedema.[17] This patient (T.G.) was in the 1925–1937 group; a review of the kidney sections in his case showed a moderate number of hyaline masses in the glomeruli.

Bence–Jones[18] reported in 1853 that the glycosuria of patients with diabetes mellitus diminished as age advanced. This has been explained on the basis of the effect of aging on the "renal threshold" for glucose.[19] The present report suggests, however, that the loss of glycosuria in many patients with diabetes of long duration is due not to an impaired excretion of glucose but to the lowered blood-sugar concentrations occurring in the patients with Kimmelstiel–Wilson lesions.

The second element in the definition of mildness of diabetes is absence of acidosis. In this regard the diabetes of the Kimmelstiel–Wilson group is certainly mild. The tables do not show vividly enough the degree of this difference among the patients with Kimmelstiel–Wilson lesions and the controls. The patients in the control groups developed acidosis repeatedly, whereas the two patients with Kimmelstiel–Wilson lesions had only a single episode of acidosis each (Case 3). The failure of the Kimmelstiel–Wilson group to develop acidosis is characteristic of the entire duration of the diabetes, but the ameliorative tendency becomes apparent only in the latter years of the diabetes.

The diabetes mellitus occurring in patients with Kimmelstiel–Wilson lesions seems to have different metabolic characteristics from those of comparable control cases. The significance of this anomaly in terms of intermediary metabolism and hormonal control is not understood, although it clearly involves both the fat and carbohydrate metabolic defects. The Kimmelstiel–Wilson lesions may represent an anatomic expression of the underlying differences in metabolism of this group. It seems unlikely that the glomerular lesions are causally responsible for the differences in metabolic characteristics. The anterior-pituitary sections were carefully investigated for aneurysmal and hyaline changes in blood vessels, in view of the observations by Friedenwald[13] that the microaneurysms in the retina and glomerulus occurring in diabetes may be part of a generalized vascular change. No vascular abnormalities were noted.

For decades physicians have described two clinical types of diabetic patients: the obese, elderly patient who does not develop ketosis and the thin young patient who easily becomes ketotic. These types have been correlated with various factors and characteristics: age,[7] constitution,[20] insulin sensitivity,[21] plasma-insulin concentration[22] and origin of diabetes (pancreatic or pituitary).[23] This report has shown that a specific type of diabetes is associated with Kimmelstiel–Wilson lesions. It would be of interest to reappraise the types of diabetes previously described in terms of the presence or absence of Kimmelstiel–Wilson lesions.

Summary and Conclusions

A study has been made of the effect of renal disease on the severity of diabetes in 190 patients who came to autopsy at the Johns Hopkins Hospital. For the purpose of a controlled comparison, these patients have been divided into three groups on the basis of their renal lesions: those with Kimmelstiel–Wilson lesions, those with other types of renal lesions and those with no renal lesion. The basal insulin requirement of the Kimmelstiel–Wilson group was fully as high as that of the two control groups. Although the diabetics with Kimmelstiel–

Wilson lesions required progressively less insulin, the diabetics without these lesions required progressively more. In some cases the improvement has been so marked that patients with previously severe diabetes have become hypoglycemic on small doses of insulin.

The virtual absence of acidosis throughout the entire duration of diabetes in patients with Kimmelstiel–Wilson lesions has not been described previously. This rarity of diabetic acidosis is so striking that it provides a clue during life to the presence of Kimmelstiel–Wilson lesions and suggests a metabolic variation from ordinary diabetes.

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THE USE OF TANTALUM MESH IN CHEST-WALL DEFECTS*

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ANY structural defect resulting from a loss of normal supporting tissues should always be repaired whenever possible. When large areas of the chest-wall framework are removed to effect radical excision of malignant tumors, it is difficult to find an adequate substitute for the bony cage. Although this in itself is an undesirable situation, more important is the fact that in certain cases serious postoperative complications may follow because of paradoxical motion that may be difficult to control by simple measures.

Recently the use of tantalum plate was suggested as a method of procedure.[1] In addition to the three cases reported in that communication, the same technic has been applied successfully in 2 other cases that presented similar problems. In each instance, the desired end result was attained. However, although it was satisfactory from many points of view, the method has been abandoned because of its obvious disadvantages, which include profuse drainage from the wound due to foreign-body reaction, the tendency of the plate to become loose and the necessity of a second operation to remove it.

It is likely that these undesirable effects result from the implantation of a fixed, unyielding foreign body in an area that is in constant physical motion. It was reasoned that the ideal substitute should possess, in addition to the inert physiochemical qualities demanded, a certain degree of flexibility, permitting limited synchronous motion with living tissue. Since tantalum plate induced an inflammatory membrane on each exposed surface, a mesh-like substance that would allow solid knitting and tissue incorporation seemed more desirable. Tantalum gauze, which has demonstrated its usefulness in abdominal surgery, seemed to be the material that would be least likely to provoke complications. We have recently had occasion to utilize this material in two cases that required extensive resection of the chest wall. In both patients the wounds healed without difficulty and have remained in satisfactory postoperative condition for periods of five and six months respectively. Observations suggest that this material is ideal for creating permanent stabilization of large chest-wall defects.

Case Reports

Case 1. L. M., a 52-year-old man, entered the Rhode Island Hospital on July 30, 1950, complaining of progressive cough and dyspnea of a year's duration and an associated 20-lb. weight loss.

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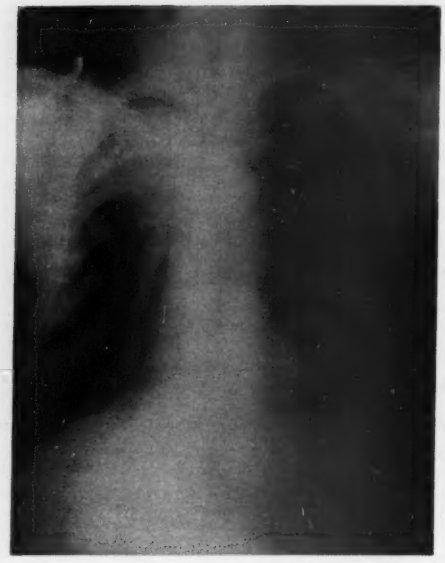

FIGURE 1. *X-ray Film of Chest in Case 1 Prior to Admission, Showing Infiltration of Right Upper Lobe.*

Physical examination revealed a well developed middle-aged man of good color who was slightly dyspneic at rest. Dullness and decreased breath sounds were present over the right upper lobe anteriorly and posteriorly. Examination was otherwise unremarkable.

Examination of the blood revealed a hemoglobin of 16.2 gm. per 100 cc. and a red-cell count of 5,070,000. Urinalysis, blood urea nitrogen, blood glucose and carbon-dioxide combining power were all within normal limits. A blood Hinton test was negative. The sputum was negative for acid-fast bacilli, and no tumor cells were seen on Papanicolaou smears. At bronchoscopy, the orifice of the right-upper-lobe bronchus was markedly narrowed and exuded purulent material, but no tumor was seen. Chest x-ray films revealed extensive right-upper-lobe infiltration consistent with a new growth.

On August 3, 1950, under endotracheal cyclopropane-ether anesthesia, the right chest was opened through a right-paravertebral incision. After excision of the 5th rib, the pleural cavity was entered and a large tumor mass occupying most of the right upper lobe was encountered. It encroached on the hilar area and extended to the upper portion of the right lower lobe. The mass was also firmly fixed to the chest wall in the posterior apical region. The lung root was evaluated, and it was possible to dissect out the vessels in spite of shortening due to tumor encroachment. In order to mobilize the right upper lobe, it was necessary to divide segments of the 2nd, 3rd and 4th ribs at their spinal attachments and in the midaxillary line, well anterior to the adherent margin of the tumor. The divided ribs with attached pleura and intercostal muscles were then resected en bloc with the entire lung. Eight hundred thousand units of penicillin in 10 cc. of saline solution was introduced into the pleural cavity. The large chest-wall defect extending from the 1st to the 6th ribs was then covered with tantalum mesh, which was sutured firmly to the intercostal muscles and fascia with interrupted sutures of No. 30 cotton. The remainder of the wound was closed in layers with interrupted cotton sutures. The patient received 2000 cc. of blood during the course of the operation, which was well tolerated. Oxygen was administered nasally for 24 hours. On the 3rd day he was able to get out of bed and was given a soft solid diet. Thoracenteses were performed on four occasions, yielding relatively small amounts of sero-sanguineous fluid. Postoperative x-ray films, in addition to showing a low level of pleural exudate, showed that the tantalum gauze was in place. The left lung field was clear and there was no shifting of the mediastinum. The sutures were removed on the 7th postoperative day, at which time the wound had healed *per primam*. There was absolutely no motion over the area of the defect. When discharged on the 15th postoperative day, the patient was entirely free of chest pain and much elated by the complete absence of cough and relief from dyspnea. The pathologist reported: "An extensive, infiltrating, highly undifferentiated adenocarcinoma with metastasis to the peribronchial lymph nodes." The patient was asymptomatic and able to pursue his regular activities for 4 months. However, he has failed to gain weight and of late has been complaining of weakness. It is highly probable that these symptoms represent recurrent disease. When recently seen, 6 months after operation, he had no pain and the chest wall was firm, solidly healed and nontender. There was negligible paradoxical motion, the excursions being less than 0.5 cm. in the center of the defect on full inspiration and forced expiration. The position of the gauze on x-ray examination remains unchanged.

CASE 2. R. G., a 77-year-old woman, entered the hospital on August 2, 1950, complaining of a lump on the right posterior chest. It had recently been growing rapidly and had become exquisitely painful. Previous biopsy was reported to show a highly undifferentiated malignant growth.

Physical examination revealed a debilitated elderly woman complaining of severe chest pain. The heart was moderately enlarged and the blood pressure 210/90. Over the right posterior thorax a grapefruit-sized mass extended from the upper border of the 7th rib to the lower border of the 11th rib. It was firm and adherent to the overlying skin and to the chest wall beneath.

Examination of the blood revealed a hemoglobin of 9.7 gm. per 100 cc. and a red-cell count of 3,050,000. Urinalysis, blood urea nitrogen and blood glucose were within normal limits. A blood Hinton test was negative.

A chest x-ray film showed clear lung fields and no evidence of rib destruction. Retrograde pyelograms, a barium-enema

FIGURE 2. *Photograph of Chest in Case 1 Five Months After Operation, Showing Cleanly Healed Incision and Almost Complete Absence of Deformity.*

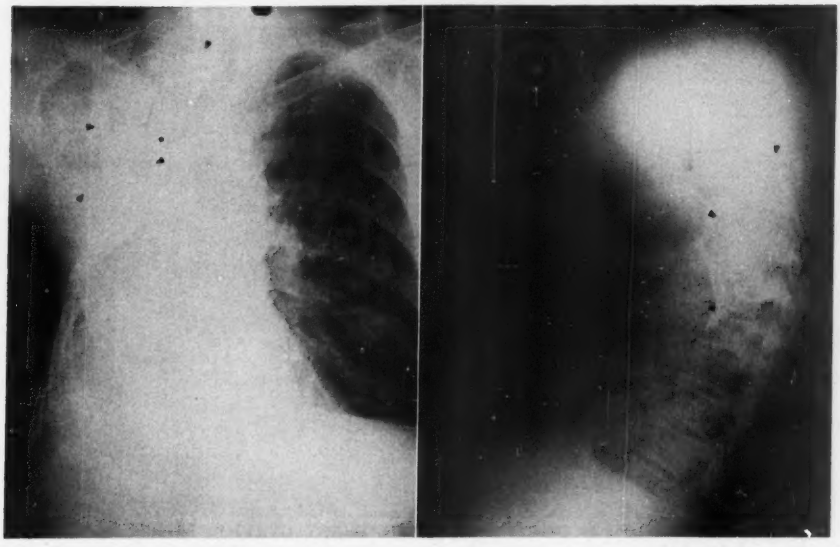

FIGURE 3. *X-Ray Films of Chest in Case 1 Two Months After Operation, Showing Tantalum Gauze in Place.*

FIGURE 4. *Photographs of Tumor in Case 2 at Time of Admission.*

examination and a gastrointestinal series failed to show a primary site of tumor formation.

On August 10, 1950, under endotracheal ether anesthesia, a large elliptical incision was made around the tumor. The excision included a liberal margin of skin (15 by 8 cm.), subcutaneous fat and muscle. In addition, long segments of the seventh, eighth, ninth, tenth and eleventh ribs, to which the tumor was firmly attached, were included with the specimen. The tumor had not extended to the deep surface of the ribs or intercostal muscles; it was therefore possible to leave the larger portion of the underlying parietal pleura. Tantalum gauze was then fitted snugly across the defect and sutured to the fascia with No. 16 cotton sutures. In addition, it was anchored with encircling sutures of No. 16 cotton to the 6th rib above and the 12th rib below.

Closure of the soft-tissue defect by simple undermining was obviously impossible. Therefore, a wide sliding flap of skin and subcutaneous fat was raised from the midposterior thorax and was utilized to permit easy closure over the tantalum gauze. The denuded donor area was covered with a split-thickness skin graft. The patient received 1000 cc. of blood during the course of the operation, which was well tolerated. She was returned to the ward in good condition.

The pathologist reported: "This is most probably a rhabdomyosarcoma, despite the absence of spider cells in their typical form and the failure to demonstrate cross striations."

There were no postoperative respiratory complications. The temperature subsided to normal on the 2nd postoperative day, and the patient remained afebrile thereafter. When the initial dressing was performed on the 8th day, slight separations of the wound edges and a small amount of serous drainage were noted. Drainage did not become purulent and ceased in about 2 weeks, by which time there was complete healing, with the exception of a small area where the split graft had failed to take. This was covered with pinch grafts.

The most gratifying features of the postoperative course were the marked lessening of pain, the freedom from pulmonary symptoms and the absence of pleural effusion.

The only serious postoperative problems stemmed directly from the patient's debilitated condition. She was reluctant

FIGURE 5. *X-Ray Films of Chest in Case 2 Two Months After Admission, Showing the Extent of the Resection and the Negligible Collapse of the Right Lung.*

to get out of bed or to help herself in any way. On a regimen of energetic supportive measures, however, she gradually gained strength and became ambulatory. At the time of discharge on the 61st postoperative day her chest wall was firmly healed and solid. The patient was seen in the Follow-Up Clinic 3 months later; she had gained considerable weight and strength and was able to care for herself. There was no evidence of recurrent disease. She complained of occasional aches and pains but had no symptoms referable to the implanted gauze. The chest wall remained firm and the scar nontender. There was negligible paradoxical motion, the excursions in the central portion of the defect being less than 0.5 cm. between full inspiration and forced expiration.

DISCUSSION

Although no previous experiences with the use of tantalum mesh for the closure of chest-wall defects had been recorded when these operations were performed, Morrow has recently reported an excellent experimental study[2] and later described its successful application in one human subject.[3] Ada and Hevenor[4] have operated on 2 additional patients, with favorable end results. The present report brings to a total of 5 the number of published cases in which the method has been successfully applied.

Morrow carried out the operation on 7 dogs, all of which survived and were later autopsied at intervals up to 229 days. The gauze was well tolerated, and no pleural fluid developed. In some areas there were adhesions to the underlying lung; in others the deep surface of the gauze was smooth and glistening, resembling parietal pleura. In 3 cases the gauze was partially torn, but the defects were bridged by dense fibrous tissue.

FIGURE 6. *Photograph of Chest in Case 2 Five Months After Operation.*

Our experience with the method closely parallels that of the other workers mentioned. The fact that one wound healed solidly, despite postoperative separation of the edges and moderate serous drainage in a debilitated elderly patient, is especially encouraging.

Relatively delicate gauze* was used in both cases. It appears that immediately after operation the gauze, snugly secured to the edges of the defect and therefore contoured by these edges, acts as an unyielding sling, contributing to the formation of a stable chest wall, purely by virtue of its tensile strength. As time passes, however, a pervading dense fibrotic wall is formed about the gauze, greatly reinforcing it and making heavy gauze unnecessary. In addition, it is an established fact that heavy gauze is more conducive to hardening and fracture.

Tantalum plate was used primarily to obviate serious postoperative problems. It appears reasonable to conclude that tantalum gauze, since it is unassociated with wound complications, is indicated when any appreciable defect is created, since it restores the normal rigidity to the chest wall. This seems more desirable than the unprotected mobile soft-tissue covering.

*Diameter = .003 inches; 50 meshes per inch.

Addendum

Since this communication was submitted for publication tantalum mesh has been used in 2 additional cases with excellent results. In both instances large segments of the anterior chest wall were resected for recurrent carcinoma of the breast.

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DEVELOPMENT OF NEUROLOGIC MANIFESTATIONS OF PERNICIOUS ANEMIA DURING MULTIVITAMIN THERAPY*

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IN SOME patients with pernicious anemia neurologic manifestations occur before significant anemia develops. Such cases have been uncommon in the past. At the Johns Hopkins Hospital in the five-year period prior to 1950, the diagnosis of pernicious anemia was established in 58 patients in whom the disease had not previously been recognized. In 8 of these patients blood values were essentially normal at the time the diagnosis was made. However, in 7 of these 8 cases anemia was known to have been present prior to admission, and there was a definite history of treatment with folic acid, liver extracts or blood transfusions. In only 1 patient was the absence of anemia not explained.

In the year 1950, 10 patients with previously unrecognized pernicious anemia were seen at this hospital. Five of these patients complained only of neurologic symptoms and were found to have little or no anemia. Because the blood values were essentially normal, the diagnosis of pernicious anemia was not always immediately apparent, and some of these patients were at first thought to have multiple sclerosis and other neurologic disorders. Careful history revealed in 2 cases that soreness of the tongue had been present at some time in the years prior to admission. One patient was known to have had a previous episode of anemia. On examination each of the 5 patients displayed the manifestations of subacute combined degeneration. Achlorhydria following the injection of histamine was demonstrated in each patient. Therapy with parenterally administered vitamin B_{12} was followed by improvement of the neurologic manifestations in these cases.

Investigation was undertaken to determine why these patients with pernicious anemia had essentially normal blood values. Recent studies have shown that the administration of folic acid can overcome the blood abnormalities of pernicious anemia while allowing the neurologic disorder to progress.[1] A high intake of folic acid might account for the normal blood values in patients who had only nervous-system changes. No one of our 5 patients was aware of having received folic acid or other specific anti-anemia treatment. However, it was learned that each patient had been taking multivitamin preparations prior to admission. It was possible to identify the multivitamin preparation used by 4 of the 5 patients, and in each case the folic-acid content was adequate to produce a hematologic remission in patients with pernicious anemia. In at least 2 cases the physician who had prescribed the vitamin capsules was unaware that the preparations contained folic acid.

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Case Reports

Case 1. E. J. K. (JHH 538898), a 53-year-old man, complained of numbness in the hands and feet and stumbling gait of one year's duration. He also noted that he frequently dropped things and that his hands and feet occasionally tingled. He complained of intermittent bloating and eructations but denied any diarrhea, vomiting or sore tongue. There was no history of anemia. For the past 2 years he had been taking multivitamin capsules* whenever he felt tired. Physical examination showed good color and a normal-appearing tongue. Neurologic examination revealed a wide ataxic gait, a slightly positive Romberg sign and diminished touch and pain sensation in both hands. Vibratory sense was intact. Laboratory examination disclosed a red-cell count of 5,600,000, a hemoglobin of 15 gm., a hematocrit of 47.9 per cent, a mean corpuscular volume of 86 cu. microns and a mean corpuscular hemoglobin of 27 micromicrogm. The mean corpuscular hemoglobin concentration was 32 per cent, the icteric index 8 and the white-cell count 9450. Gastric analysis showed no free acid in the gastric secretion after injection of histamine. The patient was given vitamin B_{12} intramuscularly and showed marked subjective improvement. The numbness and tingling in the hands and feet disappeared almost completely and the gait returned to normal. He is now able to carry on his normal activities freely.

Case 2. L. B. (JHH 525566), a 75-year-old woman, complained of stiffness of the legs and difficulty in maintaining balance. Four years before admission the patient had complained of severe weakness. She was seen by a physician, who told her that she had anemia. The cause of the anemia was not determined, but the patient was treated with liver injections and iron for 3 months and her weakness disappeared. She had no digestive or neurologic complaints. She ate large quantities of liver for 2 years, but liver-injection therapy was discontinued. For 2½ years before admission she took 8 capsules of a proprietary preparation per day.† For one year she noted "dryness and coldness" of her feet. She subsequently developed numbness and tingling of both hands and feet. For 3 weeks she had progressive ataxia, poor appetite and some weight loss. Physical examination showed no pallor, but the tongue was smooth along the edges. Neurologic examination revealed a positive Romberg sign. The gait was ataxic, and the patient could not walk without the aid of crutches. Vibratory sense was diminished below the iliac crest. Laboratory studies revealed a red-cell count of 5,000,000, a hemoglobin of 14.2 gm., a hematocrit of 45.7 per cent, a mean corpuscular volume of 92 cu. microns and a mean corpuscular hemoglobin of 28 micromicrogm. The mean corpuscular hemoglobin concentration was 31 per cent, the icteric index 6 and the white-cell count 5700. There was gastric achlorhydria after histamine injection. The patient was given vitamin B_{12} intramuscularly, after which there was marked subjective improvement. There was some return of vibratory sense, and the Romberg sign diminished in degree of sway. The patient was able to discard her crutches for a cane and within 2 months was able to walk unaided.

Case 3. C. E. (JHH 250770), a 55-year-old barber, was admitted to the Johns Hopkins Hospital complaining of progressive numbness and tingling in the arms and legs and of inability to use his hands in his work. Four years before admission the patient had noted numbness in the hands and clumsiness in cutting hair. A few months later he complained of sore tongue and tingling in his feet. He was known to have a positive serologic test for syphilis and a history of inadequate therapy with mapharsen and bismuth. A spinal-fluid Wassermann test was positive. The neurologic manifestations were attributed to neurosyphilis, and the patient was treated with 6,000,000 units of penicillin. During the next 4 years he continued to complain of numbness, sore tongue and difficulty in speaking. At various times macrocytosis of the peripheral blood was noted, but repeated blood counts showed that the patient was not anemic; the hematocrit exceeded 40 per cent. For over 3 years he had taken 6 vitamin capsules daily.‡ Physical examination showed no pallor. The tongue was red and smooth along the edges. The pupils were fixed to light but not to accommodation. There was right-facial weakness. The gait was wide-based and ataxic, and the Romberg sign was markedly positive. Vibratory sense was absent below the knees and position sense was absent in the toes. The hands were clumsy in performing simple acts. Initial laboratory studies revealed a red-cell count of 3,020,000, a hemoglobin of 9.8 gm., a hematocrit of 30.5 per cent, a mean corpuscular volume of 101 cu. microns and a mean corpuscular hemoglobin of 33 micromicrogm. The mean corpuscular hemoglobin concentration was 33 per cent and the white-cell count 6500. Gastric analysis showed no free acid after histamine injection. Sternal-marrow smears were suggestive of pernicious anemia, although no megaloblasts were seen. The patient was given vitamin B_{12} parenterally. The tongue became normal in appearance. There was a slow rise in the hematocrit, and 8 weeks after the beginning of therapy the blood values were normal. At the present time the patient is able to use barbers' implements again, although he still cannot walk normally. He has noted marked improvement in the numbness and tingling. It is evident that he had both neurosyphilis and pernicious anemia.

Case 4. R. R. C (JHH 526257), a 61-year-old man, was first seen in the out-patient department complaining of mild gastrointestinal symptoms. Physical examination, x-ray studies and routine blood counts were normal. He was thought to have moderate mental depression. He returned to the care of his physician, who prescribed 3 capsules of a vitamin preparation each day.§ Five months later he returned, complaining of weakness, tiredness and numbness in both hands and feet. Physical examination showed no pallor. The tongue was smooth. Neurologic examination showed an ataxic gait and a loss of vibratory sense in both legs. A diagnosis of multiple sclerosis was considered. The hematocrit on admission was 39.1 per cent. However, while under observation the patient developed slight anemia. Laboratory studies made 2 weeks after admission revealed a red-cell count of 3,400,000, a hemoglobin of 12.5 gm., a hematocrit of 36.9 per cent, a mean corpuscular volume of 109 cu. microns and a mean corpuscular hemoglobin of 37 micromicrogm. The mean corpuscular hemoglobin concentration was 34 and the white-cell count 4200. Gastric analysis showed absence of free acid after histamine injection. The patient was given vitamin B_{12} parenterally. There was rapid subjective improvement, and the blood values returned to normal. At the present time there is still diminished vibratory sense in the legs, but the gait is normal and the patient has no complaints.

Case 5. J. B. (JHH 403752), a 69-year-old man, complained of numbness and pins-and-needles sensation in the hands and feet of 1 month's duration. During the past year he had also noted sore tongue and sore gums, which he attributed to an ill-fitting denture. He had been taking multivitamin pills for a year. It was not possible to determine which proprietary preparation he had used. Initial physical examination disclosed no evidence of anemia. The tongue appeared normal. Neurologic examination showed impaired vibratory sense in both lower extremities, a positive Romberg sign and a bilateral positive Babinski sign. The initial hematocrit value was 42.3 per cent. Two weeks later the hematocrit was 39.8 per cent, the red-cell count was 3,440,000, the hemoglobin 13.0 gm., the mean corpuscular volume 116 cu. microns and the mean corpuscular hemoglobin 38 micromicrogm. The mean corpuscular hemoglobin concentration was 33 per cent, the white-cell count 5650 and the icteric index 7.5. No acid was present in the stomach after injection of histamine. Examination of the sternal-marrow smears was inconclusive. The patient was treated with vitamin B_{12}. His hematocrit rose to 45 per cent and the red-cell indices became normal. Neurologic examination 2 months after therapy showed improvement in perception of vibration; the Romberg sign was negative and the Babinski sign equivocal. The patient's subjective complaints of numbness disappeared, although he still described bizarre tingling in various parts of his body.

*A preparation of which each capsule contained 5 mg. of folic acid.

†Each capsule of this preparation contained 1 mg. of folic acid.

‡Each capsule contained 0.75 mg. of folic acid.

§Each capsule contained 1.7 mg. of folic acid.

Discussion

The early manifestations of pernicious anemia include weakness, vague gastrointestinal disturbances, unimpressive paresthesias and soreness of

the tongue. Patients with such complaints often take, or are given, vitamin preparations. Since folic acid has been made available it has been incorporated into dozens of proprietary vitamin products and tonics. The amount of folic acid furnished by the recommended daily dose of most of these preparations is quite adequate to overcome the blood abnormalities and to maintain normal hematopoiesis in patients with pernicious anemia. The alimentary disturbances may also be relieved by the folic acid in these preparations, but the neurologic disease is not benefited and often progresses. Patients with pernicious anemia receiving such vitamin complexes may develop progressive and severe subacute combined degeneration while the blood picture remains normal.

A survey of proprietary vitamin products widely available as of January, 1951, revealed that more than 80 contained folic acid. About 50 per cent of these preparations are advertised primarily as multivitamins and not as antianemic agents. When taken in the doses recommended by the manufacturer, these compounds provide from 0.2 to 48 mg. of folic acid daily. It has been shown that 5 mg. of folic acid taken daily will maintain a prolonged hematologic remission in patients with pernicious anemia[2]; most of these preparations provide more than 5 mg.

In view of the relatively limited occurrence of folic-acid deficiency states, it does not seem necessary or prudent routinely to employ multivitamin preparations to which folic acid has been added. However, since these mixtures are in widespread use, the physician must be especially careful to watch for the early manifestations of pernicious anemia. For example, every patient who complains of soreness or burning of the tongue should be carefully examined to exclude the diagnosis of pernicious anemia before multivitamins are prescribed. The neurologic abnormalities of subacute combined degeneration should always be attributed to pernicious anemia unless proved otherwise. The demonstration of histamine-refractory achlorhydria in a patient with this neurologic disorder is an indication for intensive therapy with vitamin B_{12}, even though the blood and bone marrow are normal. Clinical response to such therapy provides strong support for the diagnosis of pernicious anemia.

The incorporation of small amounts of vitamin B_{12} in multivitamin preparations does not protect the patient with pernicious anemia against the development of subacute combined degeneration. Vitamin B_{12} is poorly absorbed from the gastrointestinal tract in patients with this disease, and the vitamin must be given parenterally for optimal effect.

Summary

Of 10 patients with pernicious anemia seen in a one-year period at the Johns Hopkins Hospital, 5 had little or no anemia at the time that the diagnosis was established. These 5 patients complained only of the neurologic manifestations of subacute combined degeneration. The absence of anemia in these patients could be attributed to the use of multivitamin preparations containing folic acid. Since folic acid has been included in so many multivitamin preparations, it is anticipated that cases of this type will be seen with increasing frequency. Preparations containing folic acid should not be prescribed for patients whose symptoms might be attributable to pernicious anemia. Patients with the neurologic manifestations of subacute combined degeneration should be regarded as having pernicious anemia even though the blood values are normal and should be given intensive therapy with parenterally administered vitamin B_{12} or purified liver extract.

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MEDICAL PROGRESS

ANTIHISTAMINES: THEIR USE AND ABUSE*

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ANTIHISTAMINES no longer make the headlines. Now and then comments about them appear on the editorial page. More recently they have been found among the advertisements. Time is necessary for the clinical evaluation of any therapeutic agent. It is now five years since the first of these drugs became available to the practicing physician. In that period hundreds of articles, many reviews[1] and several books[2-4] have appeared discussing the chemistry, pharmacology and physiology of the antihistamines and recounting clinical observations on their effect in numerous diseases and conditions.

As with the advent of many new types of drugs, the appearance of the antihistamines was heralded as the source of a probable cure for all allergic disorders. Their field of potential action was widened by scattered reports of beneficial effects in varied branches of medicine, including suggestive evidence that the antihistamines might cure the common cold.

More up-to-date evaluation has shown that the antihistamines are of real value in the control of various types of allergic disease, as well as in some other manifestations believed to be based on histamine action. Numerous reports of clinical benefits and side-reactions of 34 commercially important antihistamines contained in some 185 proprietary antihistaminic preparations manufactured by about 85 pharmaceutical companies scattered about the world[4] make it difficult for the physician to be confident of his batting averages in knowing what preparations, if any, he should prescribe for various symptoms in his patients.

USES

The following observations are now widely accepted with regard to the likelihood of aid from the antihistamines. Seasonal hay fever heads the success list in respiratory allergy. Of its symptoms, sneezing, itching and rhinorrhea are the most readily susceptible to relief. Perennial vasomotor rhinitis is frequently benefited, more markedly so when extrinsic factors are important or when hyperesthetic symptoms predominate. Less satisfactory results may be expected when the etiology is infectious, intrinsic or unknown and when the patient complains primarily of nasal obstruction. The antihistamines may offer little aid, whatever the etiology, in long-standing cases of perennial vasomotor rhinitis due, most likely, to secondary changes in the nasal mucous membrane. Rough figures indicate that approximately 70 per cent of seasonal-hay-fever patients and 50 per cent of those with the perennial variety may expect relief from these drugs in full therapeutic doses.[5] Such good fortune cannot be anticipated by the asthmatic patient, however. Here most allergists agree that the drugs of choice are still ephedrine, epinephrine, isuprel, aminophyllin and the iodides.[2] Antihistamines are frequently employed, however, in the treatment of severe intrinsic asthma when their benefit is minimal and when their tendency to dry bronchial secretions often contraindicates their use. This does not mean that the antihistamines are not at times effective in asthma when given by mouth[6] or when administered as an aerosol, by the rectal route or intravenously.[7]

The itching dermatoses do very well with the antihistamines, particularly acute urticaria and, less dramatically, chronic urticaria[8-10] and angioedema. Serum disease is not far behind. The percentages of relief in these conditions are somewhere between 90 and 70. Variable but less satisfactory results have been reported in atopic or neurodermatitis,[10-13] in contact dermatitis[10] (by both oral and topical routes), in the itching of jaundice[14] and in pruritus ani and vulvae.[12]

The antihistamines are often helpful in motion sickness. Gay and Carliner[15, 16] reported relief of seasickness with 50 to 100 mg. of Dramamine every six hours in all but 17 of 389 soldiers at sea who developed moderate to violent symptoms of nausea and vomiting. A subsequent report[17] has indicated a high percentage of prophylactic and therapeutic relief with Dramamine in all types of motion sickness occurring on land, at sea or in the air, as well as effectiveness in patients with various types of dizziness, of labyrinthine as well as of central origin. A recent report of a Navy symposium on motion sickness[18] contains among its conclusions the following: "The most promising new development is in the use of certain of the antihistamines; the most promising remedy appears to be a combination of hyoscine hydrobromide with one of the antihistamines." Nausea and vomiting, either of pregnancy or from synthetic estrogens,[19] have been benefited by antihistamine medication, as have

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similar symptoms due to antibiotics[20] or to postoperative conditions.[21] The incidence of reactions due to sensitivity to injected agents may likewise be reduced by combining antihistamines with agents to be injected or by preceding such injections by oral administration of an antihistamine. Such procedures have been utilized in sensitivities of various types, including insulin,[22] liver extract,[23] penicillin[24] and pollen.[25] As Feinberg[2] points out, the use of antihistamines in the prevention of local and constitutional reactions in the treatment of hay fever is not indicated as a routine procedure but should be limited to those patients in whom constitutional reactions frequently occur. Large increments in the sensitizing dose on the one hand and massive doses of antihistamines on the other are not recommended for general use, as the former may result in serious reactions difficult to control and the latter in marked side-reactions. When antihistamines are given orally in conjunction with pollen therapy, it is suggested that they be given one hour prior to injection of the antigen.

The antihistamines have other less commonly appreciated uses. Parkinson's disease[26, 27] has reacted favorably to these drugs in a relatively high percentage of cases, particularly when combined with Artane or scopolamine hydrobromide.[28] The results of therapy with antihistamines in migraine have been equivocal.[9, 29] Sunburn may be prevented by the application of various antihistaminic ointments to the skin.[30] These ointments probably owe their effect to their filtering action on the erythema-producing ultraviolet rays of sunlight.[31] The antihistamines have also been employed with some success as remedies in dysmenorrhea,[32] radiation sickness,[32a] fungus infection[33] and encephalitis.[34]

The Common Cold — Use or Abuse?

At the outset it was claimed that the common cold could be aborted or cured in a high percentage of cases if antihistamines were administered shortly after the appearance of the first symptoms. This information was all that was necessary to spark a promotion program of mammoth proportions. In the fall of 1949 the Food and Drug Administration granted permission for over-the-counter sale of several of these preparations, and the race was on. Lay advertising became increasingly visible and audible, and today the "cold cures" exceed the antihistamines used in allergic conditions.[2] In many cases, however, manufacturers of antihistamines who could have promoted them for over-the-counter sale preferred to do so ethically. Sale of antihistamines increased from $2,000,000 in 1947 to $35,000,000 in 1949, the latter figure including only two months of over-the-counter sales.[4] Anahist's first month of sales promotion showed a jump from zero to $1,000,000. A vice-president of one of the large pharmaceutical companies predicted in early 1950 that the sale of all antihistamines would total about $100,000,000 in that year.[35]

What precipitated the Cold Rush to this veritable Klondike? Why has the subsequent Cold War become so hot? Let us examine the early evidence of the effect of the antihistamines on the common cold. Brewster,[36-37] using Benadryl, Pyribenzamine, Thenylene, Neoantergan and Histadyl, claimed that 90 per cent of all colds were aborted if medication was commenced within the first hour of symptoms. The findings reported by Arminio and Sweet[38] were even better, for in one series 100 per cent of their patients who began treatment within forty-eight hours responded to therapy. Gordon[39] claimed 85 per cent to 92 per cent improvement with antihistamines in 500 college students. Tebrock,[40] Phillips and Fishbein,[41] Kessler[42] and Middleton and Rider[43] also gave favorable reports. The majority of these publications have been criticized in one way or another. What are some of the criticisms? In most cases the patients have made their own diagnoses. Although there is no law against this, what one of us has not sadly noted that he is coming down with a cold in the evening only to observe that he is well without treatment on the following morning? Early symptoms of a cold, in which antihistaminic treatment is said to be most effective, are similar to and are likely to be confused with common vasomotor nasal symptoms due to allergy, to emotional disturbances[44] or to causes other than infection. In this connection, it is of interest that Gordon[39] made the observation that a surprisingly large number of those reporting to his clinic for cold treatment were allergic. In these early cold studies it has been emphasized that allergy has not been ruled out by history or by observation or considered as a possible determining factor in results. Another common criticism is that most of the early reports do not describe proper control series or adequate placebo administration. Furthermore, the Council on Pharmacy and Chemistry of the American Medical Association[45] pointed out that to secure completely objective conclusions in subsequent series the observer, as well as the patient, should be unaware of whether the patient belongs to the treatment group or the control group. Moreover, many types of agents such as vaccines, glycol vapors and even placebos have been claimed, and believed by many, to help the common cold in the past. These observations connote an element of suggestibility on the part of both physician and patient, the latter's credulity doubtless little diminished by a multi-million-dollar advertising campaign.

More recently, better controlled series have been made in attempts to meet some of these difficulties. Results of such studies are highly contradictory to those of earlier reports. Shaw and Wightman[46] gave Antistine to 228 patients and placebos to 215 others at Cornell University Medical Clinic. In

summary they stated: "As a result of this study, beneficial effect of the antihistaminic drug in the treatment of the common cold appears questionable." These authors incidentally noted that those patients with a history of allergy appeared to receive somewhat more benefit from the drug than from the placebo. Hoagland,[47] in a group of 190 soldiers, concluded that the antihistamines (Pyribenzamine and Tagathen) were no more effective in controlling colds than were the placebos. Cowan and Diehl[48] evaluated ascorbic acid alone, Thephorin alone, ascorbic acid with Thephorin and Pyribenzamine alone in rotation in the treatment of 367 supposedly nonallergic students at the University of Minnesota. It was their opinion that none of these medications had any important effect on the duration or severity of colds in this study. Lowell and his co-workers[49] conducted an excellently controlled experiment at Boston University in which 1214 subjects participated. Trimeton, Neoantergan, a placebo and Neohetramine were prescribed in rotation. Information obtained by questionnaire was tabulated on International Business Machine cards and statistically analyzed. The authors were unable to distinguish any effect of the three drugs on the common cold that differed significantly from the placebo.

A study[50] was carried out by the personnel of United States Naval Medical Research Unit No. 4 on the prophylaxis and treatment of acute respiratory diseases with antihistaminic drugs. This study was divided into four parts. In the first of these, 352 male Naval recruits received Neohetramine in 50-mg. doses twice a day. One group of equivalent size was given a placebo, and a third received no therapy. No significant difference in the incidence of infection could be determined among the three groups, nor was there evidence that the antihistamines prevented these diseases or effected any important alteration in their symptoms. In Part 2 of the study the same antihistamine and Trimeton, both in therapeutic doses, were compared with a placebo for prophylactic efficacy. It was concluded that there was no evidence of "abating" of colds or of any important alteration of symptoms or duration. In Part 3, 165 Navy Wave recruits received Neohetramine, atropine sulfate or placebo tablets in treatment starting from one to forty-eight hours after the onset of a cold. No significant statistical difference could be found in the three groups. In connection with the previously suggested hypothesis that allergy may have been a factor in the beneficial results of treatment with antihistamines in the earlier cold series, it is of interest that careful nasal examinations and eosinophil counts were made in all members of this group. It was observed that no correlation existed between eosinophil counts in these nasal smears and response to therapy. It was noted, however, that antihistaminic drugs had an atropine-like effect on the nasal mucous membrane. In Part 4, 165 volunteers took part in a prophylactic study and 370 participated in therapeutic comparison of the efficacy of a group of antihistaminic drugs as compared with placebos in the prevention or cure of the common cold. The prophylactic statistics were incomplete, but among those who took part in the therapeutic series equally beneficial results were reported from placebos and from antihistaminic drugs. This improvement was attributed to psychologic factors.

Browning[51] divided 600 freshman students into three groups and studied them for one year. Subjects in the first group were given 50 mg. of Histadyl every four hours as long as the cold symptoms persisted. Those in the second group were treated similarly with a placebo; the third group were untreated. The students who received placebos had the lowest rate of hospital care and the fewest number of colds per student, and the percentage of those who had colds was similar in all three groups. Feller and his co-workers[52] directly transmitted cold virus from a patient with a cold to 49 volunteers divided into three groups receiving Pyrrolazote, Neohetramine and a placebo respectively. Each group showed approximately 60 per cent incidence of infection as well as equal duration and severity of symptoms.

Detailed consideration has been given to these more recent carefully controlled large-scale investigations, as they provide the only available means of coming to an impartial conclusion about the clinical efficacy of the antihistamines in the prophylaxis, control and relief of the common cold. Review of the evidence obliges us to conclude with Bloomfield[53] that there is no solid evidence that the common cold is influenced by the antihistamines. There is no absolute proof of this, however, as the common cold is a symptom complex without pathognomonic objectively recognizable features. Whatever the facts, public acceptance of the antihistamines may be measured in monetary terms of nine figures annually. Realization of the lack of efficiency of these drugs in the control and treatment of the common cold should not blind us to their accepted value in allergic disorders.

Selection of Antihistamine

What is the best antihistamine? This is a common question. The answer is that there is no best drug, for there is a variable response among different persons to the same drug and in the same person to various preparations, in respect to both percentages of clinical relief and side-reactions. Such percentage figures are readily available for all the antihistamines that have come on the market, but the large number of these drugs that have similar types of action makes the problem confusing for the physician. Although action of the antihistamines is similar in type, its beneficial potency varies in different drugs. There is also variation in the intensity of

side-reactions, which in most instances is a matter of sedation. These two characteristics, potency and sedation, usually go hand in hand. There are compounds that are quite mild in these respects, such as Antistine, Neohetramine, Thephorin and Perazil, and those that are a little stronger, namely, Trimeton, Chlortrimeton, Diatrin, Histadyl, Neoantergan, Pyribenzamine and Pyrrolazote. Most potent and highly sedative are such drugs as Benadryl, Phenergan and Decapryn.[2]

The choice of drug may differ with various factors. Sedative action may be called for at night, whereas this is undesirable in the daytime. It is often advisable to try out several different preparations in order to find the most suitable one for effectiveness or lack of side-reactions in a given patient. Such characteristics soon become evident. It is seldom necessary to administer more than a few doses to learn whether the antihistamine agrees with the patient and the symptoms are controlled. If the patient cannot tell whether or not such a medication is helpful after taking it for a few days, the drug should be discontinued.

Several drugs have been used in combination with the antihistamines, either to neutralize their sedative action with a stimulant (amphetamine, ephedrine, aminophyllin or caffeine) or, more rarely, to neutralize their excitatory action with a sedative. This may sometimes be done by combining two antihistamines, but one must be sure how the patient reacts to each of the drugs individually before predicting a combined reaction. Antihistamines, though of little use alone in asthma, may be more effective when combined with ephedrine or aminophyllin.

Dosage

It is sometimes wise to start with one half the average dose in order to observe benefit and tolerance. If these are normal in small or usual dosage, larger amounts within a given range may often be taken without side-reactions.

It may be necessary to vary the dosage with the severity of symptoms; the worse the symptoms, the higher the dose; the larger the person, the larger the dose. Older persons need the same doses as younger ones but tolerate them less well. Children require 50 per cent of the normal dose or less, depending on their age. Daytime dosage may have to be smaller than at night, or a different drug may have to be employed if daytime sedation interferes with the patient's daily occupation. The average duration of effectiveness of these drugs is about four hours for any one dose. Delayed action may be secured if necessary by enteric-coated preparations. All these brief suggestions are merely generalities. They are only meant to serve as a starting point for the selection of a suitable drug and an individualized dosage in each case. Prolonged prophylactic action is not afforded by the antihistamines. A headmaster of a large boarding school was disappointed and apparently surprised to find that his annual June and July grass hay fever was not prevented by his taking daily doses of one of the antihistamines during the preceding months of February, March, April and May.

The antihistamines are blocking agents. Halpern[54] believes that their primary effect is the reduction of the permeability of the capillary wall. Even though the antihistamines influence markedly the manifestations of the antigen-antibody reaction,[55] they do not modify antibody production[56] or immunization activities in general.[57] Their effect is therefore temporary in character, making them good supplementary agents to bring brief symptomatic relief but not good substitutes for routine immunization therapy.

New antihistamines still appear and will doubtless continue to do so. Higher-than-average percentages of relief and a diminished incidence of side-effects are quoted for Ambodryl,[58] one of the more recent of these drugs. In spite of many similar claims in the past and of continuing efforts to produce the ideal antihistamine with these qualities, potency and toxicity continue to neutralize each other. A highly potent drug with very low toxicity has not as yet been produced.

Table 1. *Doses of Antihistamines for Adults.**

	Average Dose	Minimum Effective Dose	Maximum Doses in Severe Manifestations
	mg.	mg.	mg.
Antistine	100–200	50	200
Benadryl	50	25	200
Chlorcyclizine (Perazil, Di-Paralene)	50–100	25	200
Chlorothen (Tagathen)	50	25	100
Chlortrimeton	4	2	12
Decapryn	25	12.5	75
Diatrin	25–50	—	—
Histadyl (Thenylene)	50–100	25	200
Hydryllin	2 tablets	1 tablet	4 tablets
Neo-Antergan	50–100	25	200
Neohetramine	100–200	50	200
Phenergan	25	10	60
Pyribenzamine	50	25	200
Pyrrolazote	50	25	100
Thephorin	25–50	25	100
Trimeton	25	12.5	100
p-Fluorobenzyl-DPE (Lederle)	50	15	50–75
194B (White)	50	25	200

*Reprinted by permission from Feinberg, Malkiel and Feinberg.[3] P. 172.

Side-Effects and Toxicity

Side-effects of the antihistamines are common, varying from 50 per cent to 10 per cent with different compounds. Sedation is the commonest, but excitation is not unusual and occurs with most of these drugs in very large doses. The latter may be anticipated particularly in excitable patients and in young persons. Adults may exhibit excitation but tend toward central-nervous-system depression with

overdosage. Eleven deaths have been reported,[59] eight of these in children under two years of age. It is evidently not safe to leave antihistaminic pills or cold tablets around the house. In one case a child's accidental ingestion of as little as 100 mg. was followed by convulsions and death within fifteen hours.[60] Treatment of these reactions is as yet only symptomatic. Other less common side-effects are gastrointestinal upsets such as nausea, vomiting and diarrhea, vertigo, headache, dryness of the mouth and difficulty in urination. Side-effects are customarily mild and may readily be recognized as such, particularly if the patient is previously warned of their possible occurrence. More severe reactions are not unusual, however, and may necessitate discontinuation of the drug. Marked unexpected sedation may lead to embarrassment or even to danger in the use of handling machinery or vehicles of transportation.

More serious complications sometimes occur but fortunately are rare. Agranulocytosis has been described in several reports.[61-63] Hemolytic anemia was discovered in 3 cases after antihistaminic therapy for fourteen, ten and two months respectively.[64] The antihistamines may themselves act as sensitizers, although their chief function is that of combating symptoms of hypersensitivity. Manifestations are most often those of contact dermatitis following application of antihistaminic ointments and eye drops[65] but may follow oral therapy. On the basis of published statistics of reactions of one sort or another and of sales of antihistamines for all purposes, it has been estimated[66] that some 10,000,000 persons will experience some side-effects from these compounds. All physicians should therefore be aware of the potential dangers of the antihistamines, as well as of their benefits.

Conclusions

A review of five years of antihistamine therapy confirms the value of these drugs in many types of allergic disease as well as in other manifestations based on histamine action.

Evidence is weighed both for and against claims for the efficacy of antihistamines in the common cold. Recent large and carefully controlled clinical studies fail to demonstrate that antihistamines have any more effect on the prevention, relief or cure of the common cold than placebos.

Practical details concerning selection, dosage, side-effects and toxicity of antihistamines are discussed.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 37401

PRESENTATION OF CASE

A sixty-year-old woman was admitted to the hospital because of bilateral thigh and hip pain.

One year before admission the patient fell and sustained a fracture of the horizontal ramus and body of the left pubic bone. She was kept in bed for seven weeks and then gradually became ambulatory. She was relatively comfortable until six months before admission, when there was left-upper-thigh pain that was aggravated by movement and that radiated into the groin. Five weeks prior to admission similar pain developed in the right hip, and from that time on walking became impossible because of severe pain. However, she was moderately comfortable in bed.

Two years before admission she had been admitted to another hospital because of multiple joint pains. X-ray studies there showed moderate degenerative changes in both acromioclavicular joints, roughening of the cortices of both trochanters and ischial tuberosities, gallstones and a large calcium shadow in the right kidney area. A firm nodule in the lower pole of the right lobe of the thyroid was removed surgically, with a pathological diagnosis of macrofollicular thyroid tumor. The only other abnormal finding was a mild hyperchromic anemia.

For approximately five years before admission she had noted vague pains in the hands and feet, a transient "bothersome" backache and occasional pain and stiffness in the elbows and knees. The menopause had occurred ten years previously.

Physical examination revealed a thyroidectomy scar, with no palpable thyroid tissue or masses in the neck. Pelvic compression caused slight discomfort in the lower back. Both hips could be flexed passively to 90°, but any attempt at rotation or abduction produced pain in the trochanteric and hip-joint regions. Extension was complete and painless. There was no palpable bone tenderness. The legs and feet were normal. The remainder of the physical examination was noncontributory.

The temperature was 98.2°F., the pulse 72 and the respirations 20. The blood pressure was 138 systolic, 78 diastolic.

Urinalyses showed specific gravities varying from 1.006 to 1.014, +++ albumin, frequent clumps of bacteria in the sediment and beta-hemolytic streptococci on culture. Examination of the blood showed a white-cell count of 7100 with a normal differential, 10 gm. of hemoglobin and a red-cell count of 3,100,000 with normocytic, normochromic cells. The fasting blood sugar was 88 mg., the total

protein 6.5 gm. and the nonprotein nitrogen 23 mg. per 100 cc.; the sodium was 136.5 milliequiv., the chloride 108 milliequiv. and the carbon dioxide 21.2 milliequiv. per liter. The serum calcium was 14.5 mg., 13.6 mg. and 13.8 mg. per 100 cc. during the first week; subsequent determinations were in the same range. The serum phosphorus was 2.8 mg., 3.2 mg. and 2.2 mg. per 100 cc.; all subsequent determinations were below 3 mg. per 100 cc. The alkaline phosphatase was 45.6 units and 34.4

FIGURE 1.

units per 100 cc. The prothrombin time was 16 seconds (normal, 17 seconds) and the pH 7.40. Two twenty-four-hour specimens of urine for calcium excretion showed a volume of 1440 cc. with 121 mg. of calcium, or 8.7 mg. per 100 cc., and a volume of 1590 cc. with 84 mg. of calcium, or 5.4 mg. per 100 cc. Two urine samples were positive for Bence-Jones protein, and a twenty-four-hour specimen of urine with a total volume of 1600 cc. contained 0.816 gm. of total protein and 0.586 gm. of Bence-Jones protein.

X-ray films of the long bones showed extensive atrophy of all the bones, with coarse trabeculations and, in places, destruction of the cortex. The hands in particular showed a loss of bone substance from cortical bone. In many places in the hands, knees and thoracic spine there were minor degenerative changes. There was gross irregularity of the femoral necks, with fractures of the right hip, the left femoral neck and the left superior pubic ramus. A shadow of calcification was superimposed on the right kidney area. The skull bones showed a salt-and-pepper pattern throughout, with some localized areas of destruction in the frontal bone. An intravenous pyelogram visualized a calyceal stone in the lower pole of the right kidney. Renal and psoas shadows did not appear unusual. Injected dye appeared in faint concentration, which was inadequate to evaluate the appearance of the calyceal structures on either side. An x-ray film of the chest was negative for pulmonary or cardiac change. Barium-swallow examination revealed the suggestion of an extrinsic mass on the left above the clavicle, displacing the esophagus to the right (Fig. 1). As nearly as could be determined, this mass measured up to 4 cm. in diameter.

On the twenty-third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. ALFRED KRANES*: Is a macrofollicular thyroid tumor the same as a benign adenoma?

DR. DAVID KAHN: It is the same as what we call "nontoxic nodular goiter." It is benign.

DR. KRANES: The terminology of thyroid tumors seems constantly to be changing. However, the important thing is that it was benign and need not enter the differential diagnosis.

There must be some "hitch" in this case; the findings are so characteristic of hyperparathyroidism, with certain atypical features, that one wonders why one is asked to discuss it at a clinicopathological conference.

One does not have to consider the possibility of metastatic carcinoma of the thyroid, since the tumor that was removed was benign. However, that does not exclude the possibility of metastasis to the bone from some other less obvious area. But very much against that is the fact that, — at least in the description of the x-ray findings, — practically all portions of the visualized bone appeared to be abnormal.

May I see the films?

DR. JAMES J. MCCORT: Films of the skull reveal widespread demineralization of the visualized bones, which results in a finely mottled appearance. No expansion or thickening of the bone is apparent. The mandible is completely edentulous; hence we cannot deduce anything about the lamina dura. Films of the long bones and hands also reveal widespread loss of bone salts. There is softening at the end plates

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of the vertebral bodies, with protrusion of the intervertebral disks.

The kidney stone described in the protocol lies in the inferior calyx of the right kidney. It is somewhat amorphous in appearance, with a slightly irregular outline.

DR. KRANES: And the kidneys themselves?

DR. MCCORT: There is no evidence of calcification in the collecting tubules, the so-called nephrocalcinosis. Neither kidney is enlarged. The psoas muscles are symmetrical.

On the chest films both lungs are seen to be emphysematous. In addition to a slightly prominent left ventricle, there is a tortuous and sclerotic aorta. In the neck a small soft-tissue mass is seen, which displaces the trachea and barium-filled esophagus to the right of the midline (Fig. 1).

DR. KRANES: Did the barium swallow add anything to the information about the mass in the neck?

DR. MCCORT: It is extrinsic to the esophagus and contains no calcification. The measurement of 4 cm. is an approximation.

DR. KRANES: As a specific measurement was given, I had thought perhaps we could see the actual outline.

DR. MCCORT: Only the lateral margin is visible; the medial margin is represented by the edge of the displaced trachea.

DR. KRANES: With extensive metastatic skeletal malignancy, normal bone can usually be seen between the involved areas. That was not true in this case. As for the blood chemical findings in metastatic cancer, an elevated serum calcium is not uncommon, but a depressed serum phosphorus is extremely rare, although there are cases in which it has been reported. The elevated serum phosphatase is a frequent finding. Bence–Jones protein has been found in cases of widespread metastases to bone. Metastatic malignancy is therefore unlikely for two reasons: the extent of the involvement of the skeleton and the very low serum phosphorus.

The other disease to be seriously considered is, of course, multiple myeloma. The finding of Bence–Jones protein and the extensive involvement of the skeleton are very suggestive of multiple myeloma. If one knew nothing else about the patient except the bone disease and the Bence–Jones protein in the urine, a diagnosis of multiple myeloma would be correct 99 times out of 100.

A PHYSICIAN: The small bones are almost never affected in multiple myeloma.

DR. KRANES: That is true. It is usually a disease of the flat bones. There are several findings here that are not encountered in cases of multiple myeloma. One, which I do not believe I have ever seen, is the elevated serum phosphatase — nor do I recall any cases in which it was reported. Another unusual occurrence is the low serum phosphorus. Practically all the cases of multiple myeloma seen here have had a normal or slightly elevated serum phosphorus — the latter when renal insufficiency exists. There have been occasional cases in which a low serum phosphorus has been reported in myeloma. To my mind, the combination of two unusual findings practically excludes this disease.

Hyperparathyroidism is the disease of which almost all these findings are so characteristic. Hypercalcemia, hypophosphatemia, severe generalized bone disease, a stone in the right kidney and a very high alkaline phosphatase — certainly everything points in that direction, yet there are several findings that are troublesome. The first is the normal excretion of urinary calcium. On the other hand, there is some indication that it was not always normal. The kidney stone on the right suggests that the urinary calcium was higher at one time than it was while the patient was under observation. The presence of renal insufficiency might modify the usual finding of hypercalciuria, and I shall have to invoke that as the possible explanation of the normal urinary findings. I presume the patient, who was in the hospital for twenty-three days before operation, was put on a low-calcium diet before the urinary calcium determinations were made. The second point is the finding of Bence–Jones protein. Several years ago that would have disturbed me more than it does now, because there have been several cases of hyperparathyroidism in which Bence–Jones protein was found in the urine. The anemia, although it is not a common finding in hyperparathyroidism, may be found when there is extensive bone disease with fibrosis of the bone marrow or when there is renal insufficiency. I think it is reasonable to expect some degree of renal insufficiency here because of the fixed specific gravity of the urine, the slightly elevated nonprotein nitrogen and the slight acidosis — chlorides elevated, sodium and carbon-dioxide combining power depressed.

The operation, I suppose, was an exploration of the neck for the mass found on x-ray examination. On the other hand, it might have been a bone-marrow aspiration or a skeletal biopsy. I am somewhat surprised, in view of the Bence–Jones protein, the x-ray appearance and the anemia, that a bone-marrow puncture was not done. It may have been the operation referred to.

I do not see how this can be anything else but hyperparathyroidism. There are no findings that would refute such a diagnosis. The only disturbing point is that there was not more calcium in the patient's urine. I shall have to make that the diagnosis of choice.

DR. F. DENNETTE ADAMS: With multiple myeloma would you not expect a few cysts somewhere, or larger areas of localized decalcification?

DR. MCCORT: Yes; in multiple myeloma the areas of rarefaction in the bone would tend to be of varying size.

DR. KRANES: I should have mentioned in the differential diagnosis the possibility of sarcoidosis,

which occasionally can produce chemical findings somewhat like this, but there was not the slightest reason to suspect it clinically. There was nothing in the chest.

Dr. Adams: Another possibility that was not mentioned, — in which there are bone changes, mild anemia, high calcium and normal phosphorus, — is vitamin D intoxication.

Dr. Kranes: The usual findings in vitamin D intoxication, depending on how long the process has been going on, are hypercalcemia, usually a hyperphosphatemia (although there are cases in which the phosphorus is normal), increased urinary excretion of calcium, metastatic calcification to a rather marked degree in the soft tissues and, of course, kidney stones or nephrocalcinosis.

A Physician: There should not be any bone changes.

Dr. Kranes: Osteoporosis is common.

Clinical Diagnosis

Hyperparathyroidism.

Dr. Kranes' Diagnosis

Hyperparathyroidism.

Anatomical Diagnoses

Parathyroid adenoma.
Osteitis fibrosa generalisata.
(Hyperparathyroidism.)

Pathological Discussion

Dr. Kahn: Although the clinical diagnosis of hyperparathyroidism, with renal calcification and osteoporosis, was readily made after admission, for two years prior to this the patient had been seen quite regularly by a number of physicians and the diagnosis had never been suspected. She was referred here with a diagnosis of atypical Paget's disease.

Actually, two operations were performed, a few days apart. The first was a biopsy of one of the lesions in the femur. Histologically this showed osteitis fibrosa consistent with hyperparathyroidism. It is not possible to differentiate primary and secondary hyperparathyroidism on the basis of histologic study of the bone lesions, although in secondary hyperparathyroidism it is unusual to have cyst formation or pathologic fracture. The second operation was an exploration of the neck by Dr. W. Waddell. He found a tumor approximately the size of a small egg lying slightly to the left of the esophagus behind the left lobe of the thyroid. This measured 6.4 by 3 by 1.3 cm., weighed 11.5 gm. and microscopically was a typical parathyroid adenoma.

That the hyperparathyroidism was caused by this adenoma is substantiated by the postoperative course. Immediately after operation the serum calcium dropped to 5 mg. per 100 cc. and the patient had twitchings and paresthesia that had to be controlled by intravenously administered calcium. At the time of discharge on the thirteenth postoperative day the serum calcium was 7 mg. per 100 cc. In the four months since the operation there has been a gradual increase in strength and she is able to be up and about. As yet there has not been any noticeable change in the x-ray films of the bones, but in our series of cases it was found that it may take up to five years for the bone lesions to heal.

A Physician: Could she have a secondary hyperplasia with low excretion of calcium secondary to some renal disease?

Dr. Kranes: It is my impression that secondary hyperparathyroidism results in a diffuse hyperplasia of all four glands and that it is rare to find a solitary tumor.

Dr. Kahn: In hyperparathyroidism secondary to renal disease, although all four glands enlarge, in a rare case one may enlarge to a much greater extent than the others and might grossly be confused with an adenoma. Microscopically, though, it and the other glands will show the changes of secondary hyperplasia.

Dr. Kranes: As large as the one in this case?

Dr. Kahn: No. The largest of these may reach 2 cm. in their widest diameter. In this case the tumor was definitely a parathyroid adenoma.

Dr. Kranes: I think it is unlikely that the hyperparathyroidism could have been secondary to renal disease. First, the renal insufficiency was not very striking. Secondly, when hyperparathyroidism is due to chronic renal insufficiency the serum phosphorus is never low. When parathormone is injected into a normal patient it first produces an increase in the urinary excretion of phosphorus. Its primary function seems to be to depress the renal threshold for phosphorus. The rise in urinary calcium excretion comes later, and seems to be secondary. The hyperplasia of the parathyroid glands in chronic renal insufficiency is the result of the hyperphosphatemia — the body's attempt to increase phosphorus excretion. The reason I do not think that was present in this case is that the serum phosphorus was so low.

CASE 37402

Presentation of Case

A sixty-year-old man was admitted to the hospital because of hemoptysis.

Four weeks before entry the patient developed a cold, a sore throat and a cough, accompanied by the raising of small amounts of dark-red blood. At the time of the cold he had some shortness of breath but had noted no true dyspnea or orthopnea since. For the month before entry he was anorexic and lost ten pounds in weight. There was no dysphagia.

The past history and family history were negative.

Physical examination showed a well developed, well nourished man in no distress. The pupils reacted well on accommodation, but reaction to light was diminished. Examination of the lungs revealed a questionable dullness to the right of the spine for 3 cm. The breath sounds throughout the right chest were bronchial in character. The heart, abdomen and extremities were negative.

The blood pressure was 120 systolic, 80 diastolic.

Examination of the blood showed a white-cell count of 9800 with a normal differential and a hemoglobin of 13.6 gm. An electrocardiogram was within normal limits. The blood Hinton and Wassermann tests were positive.

Bronchoscopic examination revealed marked compression of the trachea and both main-stem bronchi, the pressure being from the left. The tracheal rings were compressed. The airway 2 cm. above the carina was reduced by 50 per cent and at the carinal level was no more than 30 per cent of normal on either side. The mucosa was intact. There were pulsations in the walls.

A barium-swallow examination showed a lobulated soft-tissue density in the anterior mediastinum in the region of the aortic arch. The esophagus was displaced posteriorly and to the right side (Fig. 1). The density appeared to be separate from the heart and to extend into the body of the fourth, fifth, sixth and seventh thoracic vertebras. It had destroyed the greater portion of the body of the fifth and a half of the fourth vertebra, with some anterior erosion of the body of the sixth and seventh. There was also wedging of these vertebral bodies and destruction of the intervertebral disk. Near the posterior margin of the upper third of the esophagus there were smooth pressure defects. There was also an area of bone erosion in the posterior axillary margin of the eighth rib.

On the fourth hospital day an operation was performed.

Differential Diagnosis

Dr. J. Gordon Scannell*: The patient's history is essentially negative except for what may have been a bad cold that went to his chest and was accompanied by hemoptysis four weeks before admission. Apparently the hemoptysis ceased — at least it was not mentioned again, so I wonder whether it was of great significance. At any rate, a bronchoscopic examination was made because of the bleeding, and the tracheal rings were found to be compressed by rather diffuse encroachment on the bronchial tree. The pulsation noted was probably transmitted by the aorta; this helps me very little in determining the cause of the tracheal compression.

There is certainly adequate evidence for a working diagnosis of aneurysm — namely, a mass in the region of the arch of the aorta, a positive Hinton test and eye signs that I am at a loss to interpret. For the sake of argument, there are certain things that bother one in accepting the diagnosis of aortic aneurysm. The heart was normal; there was no murmur of syphilitic involvement of the aortic valve. There was no history of syphilis. The fact that there was no pain bothers me most. It is very hard to believe that an aneurysm growing by pulsation and eroding the vertebras would do so without giving rise to considerable discomfort. Furthermore, the intervertebral disks were destroyed. I believe that one of the classic findings on x-ray examination is that the disks are spared — presumably because extrinsic pressure, especially of a pulsatile nature, tends to destroy a rigid structure and spare an elastic one. Lastly, if he had significant enlargement of the arch of the aorta I would expect him to have had more dysphagia than he showed, particularly as the lesion had gone on to erode the vertebra.

Figure 1.

May I look at the x-ray films now?

Dr. Joseph Hanelin: We were confused about the condition of the chest at the time of the examination. Certainly the changes were rather unconventional for almost any disease with which we were familiar. The mass is better localized in the midmediastinum than in the anterior mediastinum. It has resulted in destruction of the fourth, fifth and

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sixth thoracic bodies, the fourth and fifth being reduced to less than half their normal height. The intervertebral disks are markedly narrowed between those bodies. There is some evidence of erosion of the anterior upper tip of the body of the seventh thoracic vertebra. Particularly unusual is the appearance of the esophagus, which shows displacement to the right side and also pressure defects both anteriorly and posteriorly, as seen in the lateral projection. The lesion of the right eighth rib is of questionable significance, although the initial impression was that it might have represented a lytic process. However, the shadow is such that it may be a fracture that is undergoing healing. The heart is not enlarged, and the lungs seem clear.

DR. SCANNELL: Was the patient fluoroscoped?

DR. HANELIN: I believe he was, but I cannot tell you the findings.

DR. SCANNELL: The x-ray changes do not look much like those of an aneurysm. There is swelling in the region of the aortic arch, but otherwise the aorta looks pretty normal. Therefore, if I do not accept the obvious working diagnosis, the next possibility to consider is a tumor of the mediastinum. The first alternative to aneurysm would be a primary tumor, most likely a neurofibroma. In favor of a neurofibroma are the following facts. Destruction of bone is quite common with neurofibroma, particularly in the chest. With neurofibroma, bone involvement is not uncommonly found in the absence of pain. Neurofibroma is considered to be more common in the posterior mediastinum, whereas dermoid cysts are generally found in the anterior mediastinum. This is, of course, of limited use here, as the mass was in the middle mediastinum. The origin of a neurofibroma in that position, however, might easily be ascribed to the vagus or phrenic nerve — I shall say the vagus nerve, where it passed in front of the arch of the aorta. If such a tumor occurred there, it might expand in the fashion described in this case. The extension beneath the arch of the aorta should involve the left recurrent nerve. Since a neurofibroma is essentially a benign tumor, this diagnosis would be compatible with the general good health of this patient and with the total absence of symptoms except for the cold and the bloody sputum.

The hemoptysis, of course, requires explanation. However, hemoptysis is a not infrequent symptom with severe upper-respiratory infections, particularly if there is a lesion adjacent to and interfering with, but not necessarily invading, the bronchial tree.

I am bothered by the destruction of so many of the vertebral bodies, but not so much as I was before I saw the x-ray films. The destruction is quite well localized in relation to the mass. The mass noted far out in the right eighth rib may have been a healed fracture or a totally unrelated phenomenon — or, if I make the diagnosis of neurofibroma, it may have been another small neurofibroma. Since the bronchoscopic findings suggest an infiltrating lesion, if this was a neurofibroma it may have become malignant, though not necessarily so.

If it was not a neurofibroma, what else may it have been? Other benign tumors of the mediastinum occur but do not involve bone. On the other hand, cancer is almost excluded by the absence of pain in a lesion that has invaded adjacent bone. This also holds for a dermoid or teratomatous cyst that may have become malignant, and bronchogenic cysts do not extend this way. Lipomas may be similarly ruled out.

One condition must be excluded — namely, carcinoma of the lung. The patient had coughed blood, but he did not continue to do so. He had no other symptoms to suggest that diagnosis, and the bronchoscopic findings do not suggest it unless the cancer was an extensive one. Such extension should have produced hoarseness, mediastinal discomfort and back pain, and ordinarily would not be compatible with the patient's general well-being. A cytologic smear of the sputum might have been helpful.

A tumor of the lymphoma series, especially in an infiltrating lesion in the mediastinum, has to be thought of. Certainly, so far as the endoscopic findings are concerned, this could have been lymphoma. On the other hand, I believe lymphoma rarely involves bone in this fashion; when it does, it produces pain. Metastatic carcinoma is also a possibility. That also should have produced pain, and there was no evidence of a primary source. I do not see how I can support that diagnosis.

Lastly, one has to think in terms of an infectious process. If it was an infection, it was a very cold one. There was no history of tuberculosis and no history of pain, and the extension of this lesion is hardly such as one would see with a cold abscess. The laboratory findings were entirely within normal

limits. I think we can rule out an inflammatory process safely.

Therefore I shall return to my original first choice, a benign tumor of the neurofibroma series possibly arising from the vagus nerve.

Clinical Diagnosis

Syphilitic aneurysm of aorta.

Dr. Scannell's Diagnosis

Neurofibroma of vagus nerve.

Anatomical Diagnosis

Syphilitic aneurysm of aorta.

Pathological Discussion

Dr. Tracy B. Mallory: In this case we have broken the usual rule covering the selection of cases for these exercises. We have no anatomic specimen to offer as proof of the diagnosis. This patient was explored by Dr. Robert R. Linton. I am sorry that he could not be here to give us a description of his findings. Once he had entered the thoracic cavity, it was quite obvious that the lesion was an aneurysm of the aorta, from which he naturally did not care to take a biopsy. Instead he proceeded to wire it. I am going to ask Dr. Hanelin to show us the postoperative x-ray films demonstrating the coiled wire within the aneurysmal sac, which I think is quite as convincing evidence of the diagnosis as an anatomic specimen could be.

Dr. Hanelin: In these films, even at a distance, I think, one can see the coils of wire, which actually extend to the zones of destruction and to the eroded areas in the vertebral bodies (Fig. 2). The aneurysm chiefly involves the transverse portion.

Dr. Edward B. Benedict: If I had such a patient, who had a positive blood Hinton test, failure of the pupils to react to light and a similar x-ray picture, I would hesitate to do a bronchoscopy, because there is some hazard to bronchoscopy in aneurysm.

Dr. Mallory: In operating on this patient, Dr. Linton decided not to use an endotracheal tube, because of the possibility of injuring the wall of the aneurysm and producing severe intratracheal hemorrhage, so he evidently agrees with you, Dr. Benedict.

Dr. Hanelin: This might have been a particularly good case, in view of the slight doubt concerning the presence of the aneurysm, on which to do an angiocardiogram in an attempt to establish the diagnosis.

Dr. Mallory: One further piece of laboratory evidence came in, but it was received after the operation, and for that reason was not included in the protocol; that was a positive Wassermann reaction in the spinal fluid, confirming the evidence of syphilis but not altering the picture.

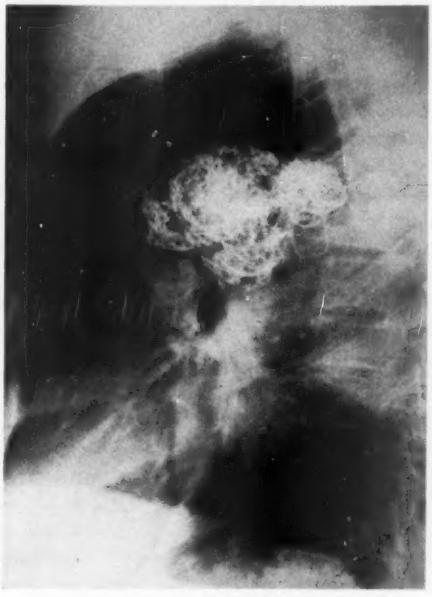

Figure 2.

Dr. Benedict: I should like to ask Dr. Hanelin if he would rule out aneurysm or thinks it is likely on the x-ray findings.

Dr. Hanelin: This case taught us a great deal. It was a most unconventional appearance for aneurysm — particularly the destructive lesions of the vertebras and the peculiar deformity of the esophagus, which was more suggestive of mediastinal infiltration than of pressure by an aneurysm. We leaned rather heavily toward a mediastinal cancer.

DR. BENEDICT: I have seen an aneurysm do just that to the esophagus, and I have seen it erode the vertebras quite extensively.

DR. HANELIN: Erosion of the vertebras is common. Actual collapse of the bodies and loss of intervertebral-disk substance are extremely rare. Generally the vertebral bodies, although eroded, maintain their height, and the disks remain intact. These films were shown to Dr. Schatzki before the operation. His first impression, — and the correct one, — was that it was an aneurysm. He had apparently seen a similar case.

ADDENDUM

DR. ROBERT R. LINTON: Dr. Scannell has considered all our preoperative diagnoses, namely, aneurysm, mediastinal tumor and tuberculosis of the spine. I myself favored the former diagnosis — especially since a tracheal tug could be demonstrated on physical examination. I do not believe that this fact was mentioned in the physical diagnosis. It seems worth while to point out at this time that in recent years, — probably because we see so few thoracic aneurysms, — this pathognomonic sign of aneurysm appears no longer to be stressed in the teaching of physical diagnosis. At any rate, very few of our interns think of testing for it today.

It was not until the thoracic cavity was actually opened and the tumor mass exposed that the diagnosis of aneurysm was positively confirmed. The preoperative x-ray finding that there was no expansile pulsation in the aneurysm did not influence my opinion particularly, as I have seen so many thoracic aneurysms that do not exhibit an expansile pulsation until they can be actually palpated through a thoracotomy incision. I used to believe it was necessary to observe an expansile pulsation by fluoroscope in order to make a diagnosis of a thoracic aneurysm. From experience I now know that this is not true. During the past several years I have wired approximately 40 aneurysms of the thoracic and abdominal aorta and have found that nearly all the thoracic aneurysms are syphilitic in origin and all the abdominal ones are arteriosclerotic.

At the time of operation, approximately 225 feet of 30-gauge stainless-steel wire was inserted into the aneurysmal sac. Particular care was taken to fill the portion of the sac that was eroding the vertebral bodies. The patient made a satisfactory convalescence and at the present time (more than a year later) is alive and well and has had no further bleeding episodes. Although not cured, the patient certainly has been given a respite from a very incapacitating and usually rapidly fatal disease.

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Established 1828

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The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

STUDENTIBUS MEDICINAE INTERNISQUE

The desire has frequently been expressed by those most closely touched by the matter that hospital interns and residents should continue to enjoy some of the initial prerogatives and concessions that had been granted to them as medical students. The interns have, it is true, taken their degrees and are doctors of medicine; they are nevertheless still in what amounts to a period of postgraduate study, and their earnings if any are little.

There are those who believe that one small breeze in particular might be tempered a little longer to the still shorn lamb; it is the purely nominal payment required for the satisfaction of having the *New England Journal of Medicine* thrust each week into their mailboxes. Approximately 5000 student subscribers constitute an amiable bloc that no one wants to ignore, and the fact that in 1950 exactly 999 of them, having graduated, shifted their subscriptions to a full paying basis constitutes another reason for considering the students among the *Journal's* best friends and most loyal supporters. Nine hundred and ninety-nine full-rate subscriptions are not to be sneezed at.

The cost of printing and mailing the *Journal*, however, has increased 10 per cent in the last year, the price of paper has taken a 20 per cent rise in slightly more than the same period of time, and other expenses have made their proportionate ascensions. This means that each student subscriber, paying half price for his subscription, has been carried at an increasing net loss to the *Journal*. Much as the student subscriber is cherished, both ends must still be made to meet.

The *Journal* has consequently prepared a compromise measure to become effective January 1, 1952, whereby it hopes to derive a little more income from this favored class of readers, and at the same time grant a little more leeway to the impecunious intern.

According to this plan all new or renewed student subscriptions received after the designated date will be at the rate of $5.00 per annum ($6.00 in Canada), *the same rate applying for the first year after graduation to all who had been subscribers as undergraduates.*

Omnia mutantur, as some Latin scholar phrased it, *nos et mutamur in illis.*

PERNICIOUS ANEMIA AND MULTIVITAMIN PREPARATIONS

Pteroylglutamic acid (folic acid) is now recognized as an important growth factor that has proved of great value in the treatment of a variety of macrocytic anemias, for some of which it appears to be highly specific.[1] In the treatment of Addisonian pernicious anemia, however, the use of the vitamin *alone*, even when large doses have been given, has failed to prevent the occurrence or progression of the specific neurologic manifestations of this disease

in spite of the production of adequate and prolonged hematologic remissions.[2, 3]

Because of the fulminating manner in which this neurologic complication may manifest itself in patients treated for pernicious anemia with folic acid, some rather broad statements and generalizations have been made in the past concerning the possible dangers of the use of pteroylglutamic acid in patients with various anemias.[4] Subsequent experience has proved that these generalizations were unwarranted.

Careful analytical reviews by Dameshek,[5] Strauss,[6] and others[1] have pointed out the evidence of the therapeutic usefulness of folic acid, and Castle[7] noted its importance, together with that of vitamin B_{12} and ascorbic acid, in normal hematopoiesis. From a review of the literature, Castle[7] summarized the status of pteroylglutamic acid in the treatment of various anemias as follows:

> . . .It has now become clearly established that pteroylglutamic acid in daily doses of one or more milligrams produces prompt increases in blood formation and at least initial clinical improvement in all varieties of nutritional macrocytic anemias, including pernicious anemia, sprue, tropical macrocytic anemia and the pernicious anemia of pregnancy and of tape worm infestation. It is highly effective in many cases of tropical macrocytic anemia and of pernicious anemia of pregnancy, or of so-called megaloblastic anemia as observed in the temperate zone in which purified liver extracts of vitamin B_{12} in usual dosage fail to be effective. Similar failure to respond to vitamin B_{12} is noted in some infants with nutritional megaloblastic anemia, but improvement is invariable with pteroylglutamic acid therapy. . . .

The earlier suspicion that folic acid may exert a direct toxic action that may cause neurologic disease appears to have been disproved.[8] Moreover, no authentic evidence has been brought forth that the use of pteroylglutamic acid has been responsible for any neurologic lesions except in patients with Addisonian pernicious anemia who failed to receive adequate doses of vitamin B_{12} or its equivalent in liver extract.

The paper by Conley and Krevans that appears elsewhere in this issue of the *Journal* re-emphasizes the importance of recognizing pernicious anemia and of treating patients with this disease specifically with injections of adequate doses of potent liver extract or vitamin B_{12} if the occurrence of subacute combined degeneration of the spinal cord is to be prevented, improved or arrested. In addition, the course of events in the cases that they present emphasizes an important feature of the indiscriminate use of multivitamin or antianemia preparations.

Many of these multivitamin preparations, as is pointed out by these authors, contain folic acid. The administration of this vitamin in the amounts provided by the dosage advocated by the manufacturers of most of these multivitamin preparations will produce general symptomatic improvement and hematologic remissions in most patients with macrocytic anemias, including those with pernicious anemia. Thus, cases of pernicious anemia may be missed and patients with this disease permitted to go inadequately treated until the glossitis and neurologic manifestations characteristic of the disease develop.

The use of most preparations that contain mixtures of effective medicaments, whether they be vitamins, antibiotics or other pharmacologically active agents, is always to be condemned. Perhaps the main reason for their condemnation in proprietary preparations is that they encourage self-treatment and provide the patient with a sense of security that keeps him from consulting a physician who, with proper care, may discover the true nature and cause of the patient's illness and apply the specific and most effective remedy. The physician, in turn, is even more remiss if he prescribes such preparations without first assuring himself that he is not dealing with a condition for which he can prescribe more specifically and more effectively. In other words, *proper diagnosis is essential for specific and optimum therapy.*

Any patient with anemia should be given careful study in an attempt to discover the character of the blood dyscrasia and its cause, whenever possible. Only in this way will it be possible to apply the proper and adequate remedy. The anemias, as pointed out in a previous editorial,[9] offer an excellent opportunity for the application of the principle of "therapeutic dissection."

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1. Present knowledge of pteroyglutamates ("folic acid"). *Nutrition Rev.* 8:260-267, 1950.
2. Ross, J. F., Belding, H., and Paegel, B. L. Development and progression of subacute combined system degeneration of spinal cord in patients with pernicious anemia treated with synthetic pteroylglutamic acid. *Blood* 3:68-90, 1948.
3. Vilter, R. W., et al. Studies on relationship of vitamin B_{12}, folic acid, thymine, uracil and methyl group donors in persons with pernicious anemia and related megaloblastic anemias. *Blood* 5:695-717, 1950.

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5. Dameshek, W. Folic acid, pernicious anemia and pendulums. *Blood* **4**: 699-701, 1949.
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9. Editorial. Folic acid and "therapeutic dissection." *New Eng. J. Med.* **242**:483, 1950.

1952 PRIZE-ESSAY COMPETITION

THE *Journal's* prize-essay competition, open to all members of the class of 1952 registered in any medical school approved by the Council on Medical Education and Hospitals of the American Medical Association, will again be concerned with the report of a clinical case personally studied by the essayist. As before, the report will be combined with a discussion of the pathologic condition represented by the case and a review of the literature, the paper following the usual form of case reports as published in the *Journal*.

The other rules of the competition are as follows:

Manuscripts are to be not more than 5000 words in length, clearly typewritten in English, double or triple spaced with references listed at the end in numerical arrangement according to the form used by the *Quarterly Cumulative Index Medicus*. They must be in the hands of the editor by March 15, 1952, and must be accompanied by a certification from the dean of the medical school concerned stating that the author is a member in good standing of the fourth-year class and specifying the expected date of graduation. All manuscripts will become the property of the *Journal*.

A cash prize of $100 will be paid for the best essay of those found to be suitable for consideration; the paper will be published in the *Journal* if the quality is considered to conform to the standards by which the editors usually judge material submitted, and the author will receive a hundred free reprints.

A second prize will consist of a two-year subscription to the *Journal*.

The editors wish to emphasize that in establishing this competition they are interested as much in encouraging good medical writing as in promoting the collection of scientific and clinical material. In judging papers that may be submitted, particular attention will accordingly be paid to clarity, simplicity and general literary excellence.

On looking over a treatise from the French of L. Tanquerel des Planches, with notes and additions on the use of lead pipe and its substitutes, by Samuel Dana, M.D., we are more than ever satisfied that there is something to be learned in regard to a variety of diseases which have their origin in the poison of lead.

Boston M. & S. J., *October 8, 1851*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

HAWAII ACCEPTS MASSACHUSETTS PREMARITAL EXAMINATION

The territory of Hawaii has agreed to accept the Massachusetts premarital-examination certificate when properly completed by a Massachusetts physician, the blood tests having been performed at the State Wassermann Laboratory and the certificate accompanied by the State Wassermann Laboratory slip bearing the name of the patient and the signature of the laboratory director.

It is therefore suggested that Massachusetts physicians add Hawaii to the list of those states accepting the Massachusetts premarital certificates under the conditions stated above (*New Eng. J. Med.* **244**:194-196, 1951).

CORRESPONDENCE

DEPRIVATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held on September 11, it was voted to revoke the registration of Dr. Jacob P. Norman, of Northampton, because of ill health.

ROBERT C. COCHRANE, M.D., *Secretary*
State House
Boston

NOTICES

PHYSICAL THERAPISTS FOR CARE OF PATIENTS WITH POLIOMYELITIS

Physicians may obtain information concerning qualified physical therapists available for patients in the convalescent stage of poliomyelitis from the following members of the American Physical Therapy Association: Connecticut, Mrs. Leonora Grissell, Route 1, Elmwood (telephone, Hartford 3-4407); Maine, Miss Lois Burns, Hyde Memorial Hospital, Bath; Massachusetts, Mrs. Nina G. Nichols, 1940 Commonwealth Avenue, Brighton (telephone, Kenmore 6-9200 [days], Algonquin 4-6685 [evenings]), Mrs. Mary T. Hynes, 9 Perkins Terrace, Worcester (telephone, Worcester 3-5213), and Mrs. Ruth S. Whitman, 47 Fenway Drive, Springfield (telephone, Springfield 7-0572); New Hampshire, Miss Mary Bullock, R.F.D. 4, Concord; Rhode Island, Miss Helen Babcock, 12 Portland Street, Providence; and Vermont, Miss Lillian Kron, 342 Pearl Street, Burlington.

NEW ENGLAND DEACONESS HOSPITAL CLINICS

The schedule for the weekly clinical meetings of the New England Deaconess Hospital is as follows:

October 12: Tuberculosis and Diabetes — Drs. Stanton and Root.
October 19: Neuropathy — Drs. Page and Marble.
October 26: Thyroidism and Diabetes — Drs. Hyman and White.
November 2: The Pituitary Gland and Diabetes — Drs. Kenny and Root.
November 9: Skin, Necrobiosis and Diabetes — Drs. Brown and Bradley.
November 16: Lipemia and Hypercholesterolemia and Diabetes — Drs. Higgins and Marble.
November 23: Lipoproteins of Gofman — Drs. Keiding and Root.
November 30: Glucose-Tolerance Tests and Diabetes — Drs. Dickson and Bradley.
December 7: Pregnancy — Drs. Story and White.
December 14: Renal Glycosuria — Drs. Stanton and Marble.
December 21: Childhood Diabetes — Drs. Brown and White.
December 28: Insulin Allergy and Lipodystrophy — Drs. Page and Marble.
January 4: Adenoma of Islets of Langerhans. Neurogenic Hypoglycemia — Drs. Hyman and Marble.

The purpose of these meetings, which are held every Friday at 8:15 a.m. in the Baker Clinic, is to stimulate questions and discussion by the physicians present. Physicians and nurses from other hospitals are invited to attend.

HARVARD SCHOOL OF PUBLIC HEALTH

The Harvard School of Public Health announces that the Cutter Lecture on Preventive Medicine, initiated in 1912, will be held in Amphitheatre D of the Harvard Medical School on October 15 at 5 p.m. Dr. Dugald Baird, Regius Professor of Midwifery at the University of Aberdeen, Scotland, will speak on "Preventive Medicine in Obstetrics." The medical profession, medical and public-health students and other interested persons are cordially invited to attend.

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held on Tuesday, October 16, at 12 m., at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston. Dr. Hugh P. Greeley, of the Department of Internal Medicine of the Lahey Clinic, will speak on "Geriatrics."

All interested physicians are invited to attend.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

A meeting of the Middlesex South District Medical Society will be held at Margaret Jewett Hall, Mount Auburn Hospital, Cambridge, on Wednesday, October 17.

PROGRAM

12:00 m. "Pregnancy for Cardiacs." Dr. Burton F. Hamilton, consultant in cardiology, Boston Lying-in Hospital.

"The Use and Choice of Cesarean Section — A Personal Experience with 240 Extraperitoneal and Intraperitoneal Sections." Dr. Cornelius T. O'Connor, senior visiting obstetrician, Mount Auburn, Cambridge City and St. Elizabeth's hospitals.

"Vaginal Hysterectomy — A Description of Its Advantages and Review of 129 Cases." Dr. Alexander A. Levi, instructor in obstetrics, Tufts College Medical School.

1:00 p.m. Luncheon.

HAMPDEN DISTRICT MEDICAL SOCIETY

The Hampden District Medical Society will hold a dinner meeting jointly with the Woman's Auxiliary at the Hotel Kimball, Springfield, on Tuesday, October 23, at 6:30 p.m.

MEDICOMILITARY SYMPOSIUM

The United States Naval Hospital at Chelsea, Massachusetts, will present a symposium on military medicine during the week of October 29. Members of the medical profession and allied sciences are invited. Advance programs may be obtained by writing to the District Medical Officer, First Naval District, 495 Summer Street, Boston, Massachusetts.

SALMON MEMORIAL LECTURES

Dr. Arthur Ruggles, of Providence, Rhode Island, will deliver the Salmon Memorial Lectures at the New York Academy of Medicine on November 7, 14 and 20. The general topic of the lectures will be "The Place and Scope of Psychotherapy."

ROCKY MOUNTAIN HARVARD MEDICAL SCHOOL ALUMNI ASSOCIATION

The fourth annual Harvard Lecture of the Rocky Mountain Harvard Medical School Alumni Association will be delivered by Dr. William B. Castle, director of the Thorndike Memorial Laboratory and professor of medicine at Harvard Medical School, on Friday afternoon, November 9, at 5:00 p.m. The lecture will be given in the Denison Auditorium of the University of Colorado Medical Center, Denver, Colorado.

Dr. Castle will speak on "Red-Cell Destruction in Hemolytic Anemias." Physicians, medical students, nurses and other interested persons are cordially invited to attend.

SPRINGFIELD ACADEMY OF MEDICINE

A meeting of the Springfield Academy of Medicine will be held in the Woman's Club Building, 43 Spring Street, on November 13, at 8:30 p.m. Dr. Isidore Snapper, clinical professor of medicine at Columbia University, will speak on the subject "Medical Diseases of the Bones."

AMERICAN ACADEMY OF DENTAL MEDICINE

The American Academy of Dental Medicine will hold its midwinter meeting and luncheon at the Hotel Statler in New York City on Sunday, December 2, at 12:30 p.m. A business meeting for members and delegates will be held at 10 a.m.

Round-table discussions on dental and medical subjects will follow the luncheon. All members and interested dentists and physicians are invited. Programs and reservations may be obtained by writing to Dr. William M. Greenhut, 124 East 84th Street, New York 28, New York.

VAN METER PRIZE AWARD

The American Goiter Association again offers the Van Meter Prize Award of $300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the association, which will be held in St. Louis, Missouri, May 1, 2 and 3, 1952, provided essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length and must be presented in English; a typewritten, double-spaced copy in duplicate must be sent to the corresponding secretary, Dr. George C. Shivers, 100 East Saint Vrain Street, Colorado Springs, Colorado, not later than March 1, 1952. The committee reviewing the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the Prize Award Essay by the author, if it is possible for him to attend. The essay will be published in the annual *Proceedings* of the association.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 9. Springfield Academy of Medicine. Page 350, issue of August 30.

OCTOBER 9. Joint meeting of the New England Society of Anesthesiologists and the Harvard Medical Society. Page 512, issue of September 27.

OCTOBER 10. Northeastern New York Radiological Society. University Club, Albany, New York.

OCTOBER 11. The Treatment of Migraine. Dr. John R. Graham. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

OCTOBER 12–JANUARY 4. New England Deaconess Hospital Clinics. Notice above.

OCTOBER 15. Harvard School of Public Health. Notice above.

OCTOBER 16. South End Medical Club. Notice above.

OCTOBER 17. Middlesex South District Medical Society. Notice above.

OCTOBER 19. Conference on Alcoholism. Page 512, issue of September 17.

OCTOBER 20–25. American Academy of Pediatrics. Royal York Hotel, Toronto, Ontario, Canada.

OCTOBER 22–24. American Association of Blood Banks. Page 316, issue of August 23.

(*Notices concluded on page xi*)

DR. WILLIAM B. TERHUNE and THE SILVER HILL FOUNDATION

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(1) Hanson, I. R. and Hingson, R. A., *Current Researches in Anesthesia and Analgesia*, 29:136 (May-June) 1950.

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NOTICES (*Concluded from page 548*)

October 22–27. Medicomilitary Symposium. Page 234, issue of August 9.

October 23. Hampden District Medical Society. Page 548.

October 29. New York Institute of Clinical Oral Pathology. Page xv, issue of June 14.

October 29. Medicomilitary Symposium. Page 548.

October 29–November 2. American Public Health Association. Page 316, issue of August 23.

October 31. New England Obstetrical and Gynecological Society, Hotel Somerset, Boston.

November 2 and 3. Eastern Section, American Trudeau Society. Page 350, issue of August 30.

November 4 and 5. American Society for the Study of Arteriosclerosis. Page xv, issue of July 12.

November 5–9. American College of Surgeons. Page 388, issue of September 6.

November 7. Salmon Memorial Lecture. Page 548.

November 7–9. New England Postgraduate Assembly. Hotel Statler, Boston.

November 7–19. Pan-Pacific Surgical Association. Page 820, issue of May 24.

November 9. Rocky Mountain Harvard Medical School Alumni Association. Page 548.

November 13. Springfield Academy of Medicine. Page 548.

November 14. Salmon Memorial Lecture. Page 548.

November 14. Northeastern New York Radiological Society. University Club, Albany, New York.

November 20. Salmon Memorial Lecture. Page 548.

December 2. American Academy of Dental Medicine. Page 548.

December 11–19. International Congress on Mental Health. Page xiii, issue of July 26.

December 14 and 15. Association for Research in Nervous and Mental Disease. Page 958, issue of June 21.

May 1–3. American Goiter Association. St. Louis, Missouri.

July 8–11, 1952. Thirteenth British Congress of Obstetrics and Gynaecology. Page xv, issue of December 14.

July 14–19, 1952. International Congress of Physical Medicine. Page 998, issue of June 28.

District Medical Societies

HAMPDEN

October 23. Hotel Kimball, Springfield. 6:30 p.m.

HAMPSHIRE

November 7. Northampton State Hospital, Northampton.

January 2. Veterans Hospital, Northampton.

March 5. Cooley-Dickinson Hospital, Northampton.

May 7. Annual Meeting. Jones Library, Amherst.

MIDDLESEX SOUTH

October 17. Mount Auburn Hospital, Cambridge. 12:00 m.

Calendar of Boston District for the Week Beginning Thursday, October 11

Thursday, October 11

*9:00–10:00 a.m. Grand rounds. Robert Breck Brigham Hospital.

Friday, October 12

*8:15 a.m. Clinic. New England Deaconess Hospital.

*9:00 a.m.–12:00 m. Combined medical and surgical staff rounds. Peter Bent Brigham Hospital.

*10:00 a.m. Surgical clinic. South End Health Unit, 57 East Concord Street, Boston.

12:00 m.–1:00 p.m. Clinicopathological conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

*1:30 p.m. Tumor clinic. Outpatient Department, Mount Auburn Hospital, Cambridge.

Monday, October 15

*11:30 a.m.–12:15 p.m. Clinical conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological conference. Main Amphitheatre, Peter Bent Brigham Hospital.

*5:00 p.m. Cutter Lecture on Preventive Medicine. Amphitheatre D, Harvard Medical School.

Tuesday, October 16

*12:00 m. South End Medical Club. Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

Wednesday, October 17

12:00 m. Middlesex South District Medical Society. Mount Auburn Hospital, Cambridge.

*Open to the medical profession.

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Index to Advertisers

	PAGE
ABC Pregnancy Tests Laboratory	viii
Astra Pharmaceutical Products, Inc.	ix
Chester A. Baker Laboratories, Inc.	vii
Baldpate, Inc.	x
Boston Diagnostic Clinic	x
Boston Medical Supply Company	viii
The Coca-Cola Company	vii
Crane Discount Corporation	x
David Memorial Nursing Home	x
Electroencephalographic Laboratory, Inc.	viii
John B. Flaherty Company, Inc.	vii
Glenside, Inc.	x
Hanover House, Inc.	x
Leary Laboratory	viii
Eli Lilly and Company	After viii
Mason Drug Company	vi
Mead Johnson and Company	Back Cover
The Medical Protective Company	vi
Norfolk County Trust Company	vii
Perkins School	x
Physicians Laboratory Service	viii
Professional Service Company	vii
Ring Sanatorium	x
Sandoz Pharmaceuticals	vi
W. B. Saunders Company	Front Cover
Schieffelin and Company	iii
The Silver Hill Foundation	ix
The Upjohn Company	v
The Wander Company	iv
Washingtonian Hospital	xi
Wiswall Sanatorium	x
Woodside Cottages, Inc.	x

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